Indian Journal of Anesthesia and Analgesia

Aims and Scope

The Indian Journal of Anesthesia and Analgesia (IJAA) is official peer-reviewed scientific journal addresses all aspects of anesthesia practice, including anesthetic administration, pharmacokinetics, preoperative and postoperative considerations, coexisting disease and other complicating factors, cost issues, and similar concerns anesthesiologists contend with daily. The Journal seeks a balance between outstanding basic scientific reports and definitive clinical and management investigations. The Journal welcomes manuscripts reflecting rigorous analysis, even if unusual in style and focus.

Readership: Anesthesiologists, Critical Care Physicians and Surgeons.

Office of Publication: Red Flower Publication Pvt. Ltd., 48/41-42, DSIDC, Pocket-II
Mayur Vihar Phase-I, Delhi – 110 091(India), Phone: 91-11-22754205, 45796900, Fax: 91-11-22754205
E-mail: info@rfppl.co.in, Website: www.rfppl.co.in

Copyright Information

For Authors

As soon as article is accepted for publication, authors will be requested to assign copyright of the article (or to grant exclusive publication and dissemination rights) to the publisher (respective the owner if other than Red Flower Publication Pvt. Ltd.). This will ensure the widest possible protection and dissemination of information under copyright laws.

More information about copyright regulations for this journal is available at www.rfppl.co.in

For Readers

All the advice and information in this journal are believed to be true and accurate at the date of its publication. Neither the editors, nor the publisher can accept any legal responsibility for any errors or omissions that may have been made. The author is totaly resposible for any error or omission in the article. The publisher makes no warranty, express or implied, with respect to the material contained herein.

All articles published in this journal are protected by copyright, which covers the exclusive rights to reproduced and distribute the article (e.g. as offprints), as well as all translation rights. No material published in this journal may be reproduced photographically or stored on microfilm, in electronic databases on video disks, etc, without obtaining written permission from the publisher (respective the copyright owner if other than Red Flower Publication Pvt. Ltd.). The use of general descriptive names, trade names, trademarks, etc., in this publication, even if not specifically identified, does not imply that these names are not protected by the relevant laws and regulations.

Journal Website

http://rfppl.co.in/about_journal.php?jid=24

Subscription Information

The Indian Journal of Anesthesia and Analgesia is published four times a year.

Volume 6 (6 issues) will be published in 2019 pISSN: 2349-8471, eISSN: 2455-6238

For information on subscription rates please contact

Subscription and Marketing Manager
Red Flower Publication Pvt. Ltd.
48/41-42, DSIDC, Pocket-II
Mayur Vihar Phase-I
Delhi - 110 091(India)
Phone: 91-11-45796900, 22754205, 22756995
sales@rfppl.co.in

The journal is distributed free of cost to members of editorial board. Institutional subscription rates (India) INR 7500 and (other countries) USD586.

All correspondence regarding individual and society subscriptions, subscription rates for 2019 and advertisements should be addressed to: info@rfppl.co.in.

Advertisement

E-mail: sales@rfppl.co.in.

Disclaimer

Red Flower Publication Pvt. Ltd. publishes advertisement in this journal reliance upon the responsibility of the advertiser to comply with all legal requirements relating to the marketing and sale of products or services advertised. Red Flower Publication Pvt. Ltd. and the editors are not responsible for claims make in the advertisement published in the journal. The appearance of advertisements in Red Flower Publication Pvt. Ltd. publications does not constitute endorsement, implied or intended, of the product advertised or the claims make for it by the advertiser.

The views expressed in this publication do not necessarily reflect those of Red Flower Publication Pvt. Ltd.

Red Flower Publication Pvt. Ltd. do not endorse the quality or the value of the advertised/sponsored products described therein.

INDIAN JOURNAL OF ANESTHESIA AND ANALGESIA

January - February 2019
Volume 6 Number 1 (Part - II)

Contents

Original Research Articles

Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(1) (Part - II): 189-196
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.27

Comparison of Laryngeal Mask Airway Proseal and Supreme in Patients Posted for Elective Surgeries Under General Anaesthesia: A Randomised Clinical Trial

Chhaya Joshi[1], Preetham C[2], Archana E[3], SY Hulakund[4]

[1]Professor [3]Assistant Professor [4]Professor and Head, Dept. of Anesthesiology, SN Medical College, Bagalkot, Navanagar, Karnataka 587102, India. [2]Associate Specialist, Dept. of Anesthesiology and Critical Care, Tata Main Hospital, Jamshedpur, Jharkhand 831001, India.

Abstract

Background: In spite of tremendous advances in contemporary anesthesia practice, airway management continues to be of paramount importance to anesthesiologist. Hemodynamic changes are the major undesirable consequences of endotracheal intubation and laryngoscopy. The supraglottic airway device is a novel device that fills the gap in airway management between tracheal intubation and use of face mask. In view of this, the present study was undertaken to compare the performance of two supraglottic airway devices LMA supreme and LMA proseal. *Methodology*: Sixty ASA I-II patients scheduled for elective surgeries under general anaesthesia were randomised into two groups of 30 each. In Group S (n=30) LMA supreme and Group P (n=30) LMA proseal were used respectively. Both the devices were compared in relation to Ease of insertion assessed in terms of attempts taken and duration, Oropharyngeal leak pressure (OLP), Intracuff pressure(ICP), Ease of passing gastric tube and device related postoperative complications. *Results*: The insertion attempts were similar between two groups. Time taken to provide an effective airway was less in LMA supreme (Group S; 15.9 2.5 Group P; 17.8 1.6) p (0.001). OLP was significantly less in LMA supreme at 1, 15 and 30 min during anesthesia (Group S; 25.2 1.2, 22.8 1.3, 21.1±.9, Group P; 27.5±1.2,25.6±1.5,23.3±1.1) p (<0.05). ICP increased significantly in proseal LMA at 15 and 30 min during anesthesia (Group P; 68.3±1.3,76.8±2.6, Group S; 63.4±1.1, 68.3±1.32) p (<0.05). There was no significance difference in passing gastric tube and device related complications between both groups. *Conclusion*: Our finding suggested that LMA supreme was better in term of ease of insertion but LMA proseal had better OLP inspite of increase in ICP. Ease of passing gastric tube was similar in both. The complications of usage of LMA are minimal and similar in both the devices.

Keywords: Laryngeal mask airway; Proseal LMA; Supreme LMA.

How to cite this article:

Chhaya Joshi, Preetham C, Archana E et. al. Comparison of Laryngeal Mask Airway Proseal and Supreme in Patients Posted for Elective Surgeries Under General Anaesthesia: A Randomised Clinical Trial. Indian J Anesth Analg. 2019;6(1):189-96.

Introduction

In spite of tremendous advances in contemporary anesthesia practice, airway management continues to be of paramount importance to anesthesiologist. Till date, the cuffed endotracheal tube was considered as gold standard for providing a safe glottic seal [1].

Respiratory morbidities are the most common anaesthesia related complications, following dental

Corresponding Author: Preetham C, Associate Specialist, Dept of anesthesiology and critical care, tata main hospital, Jamshedpur, Jharkhand 831001, India.

E-mail: preetham.bengaluru@gmail.com

Received on 31.10.2018, **Accepted on** 03.12.2018

damage during endotracheal intubation. The three main causes of respiratory related morbidities are inadequate ventilation, oesophageal intubation and difficult tracheal intubation. Difficult tracheal intubation accounts for 17% of the respiratory related injuries and results in significant morbidity and mortality. In fact up to 28% of all anaesthesia related deaths are secondary to inability to mask ventilate or intubate [2].

Laryngoscopy and endotracheal intubation produce reflex sympatho-adrenal stimulation and are associated with raised levels of plasma catecholamines, hypertension, tachycardia etc. [3]. Airway devices can be classified as intraglottic and extraglottic airway devices, which are employed to protect the airway both in elective as well as emergency situations [4].

The supraglottic airway device is a novel device that fills the gap in airway management between tracheal intubation and use of face mask. Dr Archie Brain a British anaesthesiologist, for the first time introduced the laryngeal mask airway designed to be positioned around the laryngeal inlet that could overcome the complications associated with endotracheal intubation, and yet be simple and atraumatic to insert. Careful observations and clinical experience have led to several refinements of Brain's original prototype leading to development of newer supraglottic airway device with better features for airway maintenance [5].

The primary limitation of the laryngeal mask airway (LMA) is that it does not reliably protect the lungs from regurgitated stomach contents, although it may act as a barrier at the level of the upper oesophageal sphincter if it is correctly positioned. The incidence of aspiration with the LMA has been estimated at 0.02%, which is similar to tracheal intubation in elective patients [6].

Proseal laryngeal mask airway has a dorsal cuff, in addition to the peripheral cuff of LMA, which pushes the mask anterior to provide a better seal around the glottic aperture and permits high airway pressure without leak. The drain tube parallel to the ventilation tube permits drainage of passively regurgitated gastric fluid away from the airway and serves as a passage for gastric tube [7].

A new laryngeal mask airway, LMA Supreme allowing gastric drainage has become available for clinical use. The LMA supreme is a latex free laryngeal mask airway, made of medical grade PVC (Poly vinyl chloride). The firm, elliptical and anatomically shaped airway tube facilitates easy insertion, without placing fingers in patient's mouth or requiring an introducer tool for insertion. It enables passive drainage or active drainage of gastric contents independent of ventilation with significantly lower postoperative pharyngolaryngeal morbidity [8].

There are numerous literature on comparison between these two supraglottic airway devices with contradictory results. The main aim of this study is to compare the clinical efficacy of LMA Proseal and LMA Supreme for ease of insertion and airway sealing pressure in anaesthetized and paralyzed adult patients undergoing elective surgeries. Other parameters like intracuff pressure, ease of passing gastric tube and device related post operative complications were also noted.

Materials and method

The study was undertaken after obtaining ethical committee clearance as well as informed consent from all patients. Sixty patients aged 18-60 years scheduled for various elective surgical procedures undergoing general anaesthesia belonging to ASA class I and II were included in the study. Those with mouth opening < 2 cm, BMI > 30 kg/m^2 upper respiratory tract infection, increased risk of aspiration (GERD, hiatus hernia, and pregnancy), cervical spine fracture or instability were excluded.

Sample size calculation was done using open epi software. It was a prospective randomised clinical study.

Sixty (60) patients scheduled for different elective surgeries under general anaesthesia were randomly allocated to one of the two groups of 30 patients each group. Allocation into two groups was done by computer generated randomization table.

Group S- Patients were inserted with LMA Supreme (n=30)

Group P- Patients were inserted with LMA Proseal (n=30)

Pre-anaesthetic evaluation was done on the evening before surgery. All patients included in study were kept nil per mouth for six hours prior to surgery.

On arrival to the pre-anaesthetic area patients were secured with IV cannulation, injection metoclopramide 10 mg and injection ranitidine 50 mg was injected IV 30 min before expected time of intubation.

Then the patient shifted to operating room, Ringer lactate infusion was started. The patient's head was placed on a soft pillow of 10 cms height before induction of anaesthesia with the neck flexed

and head extended. The patients were connected to multiparameter monitor which records heart rate, non-invasive blood pressure, et CO_2 and continuous ECG monitoring and oxygen saturation.

Patients were preoxygenated for 3 minutes, injection glycopyrolate 0.005 mg/kg iv, injection midazolam 0.05 mg/kg iv, injection fentanyl 2 µg/kg iv was injected as premedication just before induction. Patienst were induced by injection propofol 2.5 mg/kg iv and injection vecuronium 0.1 mg/kg iv.

After adequate depth of anesthesia was achieved, device was inserted after lubrication with water based jelly by the anaesthesiologist experienced in both device insertion.

In group P, the LMA proseal was inserted according to manufacturer's instruction manual. A size 3, 4 or 5 was used according to weight and cuff was inflated to 20 ml, 30 ml, 40 ml for size 3, 4, 5 respectively as recommended by manufacturer.

Fig. 1: LMA Proseal inserted in patient

For patients of group S, the LMA Supreme size 3, 4, 5 was inserted according to the weight and manufacturer's instructions, cuff was inflated to 30 ml, 45 ml, and 45 ml respectively.

Fig. 2: LMA Supreme inserted in patient

An effective airway was confirmed by bilateral symmetrical chest movement on manual ventilation, square wave capnography, no audible leak of gas and lack of gastric insufflations. If it is not possible to insert the device or ventilate through it, two more attempts of insertion were allowed. If placement fails after three attempts, the case was abandoned and the airway was maintained through other airway device as suitable and this case was considered as failed attempt Both the devices were fixed by taping the tube to the chin and well lubricated gastric tube was introduced in to the stomach.

Patients were maintained with nitrous oxide, oxygen mixture and isoflourane connected to dragger fabius machine and put on Pressure Control Volume mode and intermittent boluses of vecuronium administered intravenously.

Fig. 3: Anaesthesia workstation

At the end of operation, anesthetic agent was discontinued, reversed with injection glycopyrolate 0.01 mg/kg iv, injection neostigmine 0.05 mg/kg iv allowing smooth recovery of consciousness. The device was removed after the patient regains consciousness and breathes spontaneously and responds to verbal commands to open the eye. Blood staining of device, trauma to mouth, tooth or pharynx was noted.

Parameters measured

1. Ease of insertion assessed in terms of number of attempts taken to insert the device and duration (time from picking up the device until attaching it to the breathing system in seconds).

2. Oropharyngeal leak pressure was determined by closing the expiratory valve of the circle at

a fixed gas flow of 3 litre/min, and noting the airway pressure in the anesthetic breathing system(maximum allowed is 40 cm H_2O) at which audible gas leak occurred into the mouth.

3. Intracuff pressure (measured by handheld pressure guage).

4. Ease of passing gastric tube-easy, difficult, failed.

5. Incidence of airway related complications caused by supraglotic device Post-extubation cough, breath holding, laryngospasm, presence of blood on the SLMA or PLMA, lip and dental injury.

Statistical Analysis

Statistical analysis was done using SPSS software 11.0. Data obtained is tabulated in the Excel sheet analysed.

All values are expressed as mean±standard deviation. Chi-square test for proportions in qualitative data. Student's unpaired t– test for Quantitative data. $p < 0.05$ was considered statistically significant.

Results

Table 1: Showing types of surgical procedure

Sl. No	Type of surgical procedures	Group S	Group P
		No. of Patients	No. of Patients
1	Lap appendicectomy	6	9
2	Lap cholecystectomy	9	5
3	Modified mastectomy	1	3
4	Fibro adenoma of Breast	5	3
5	Hernia	5	3
6	Burns debridement	0	4
7	Hemangioma cheek	1	1
8	Pleomorphic adnoma	1	0
9	Tubectomy	1	0
10	Axillary mass	1	0
11	Phyllodes tumour	0	1
12	Debridement upper limb	0	1
	Total	30	30

Table 2: Showing number of attempts taken to insert device in each group

Insertion attempts	Group S		Group P	
	No. of patients	%	No. of patients	%
First Attempt	28	93	27	90
Second Attempt	02	07	03	10
Third Attempt	00	00	00	00
Total	30	100	30	100

X^2=0.21 P=0.64

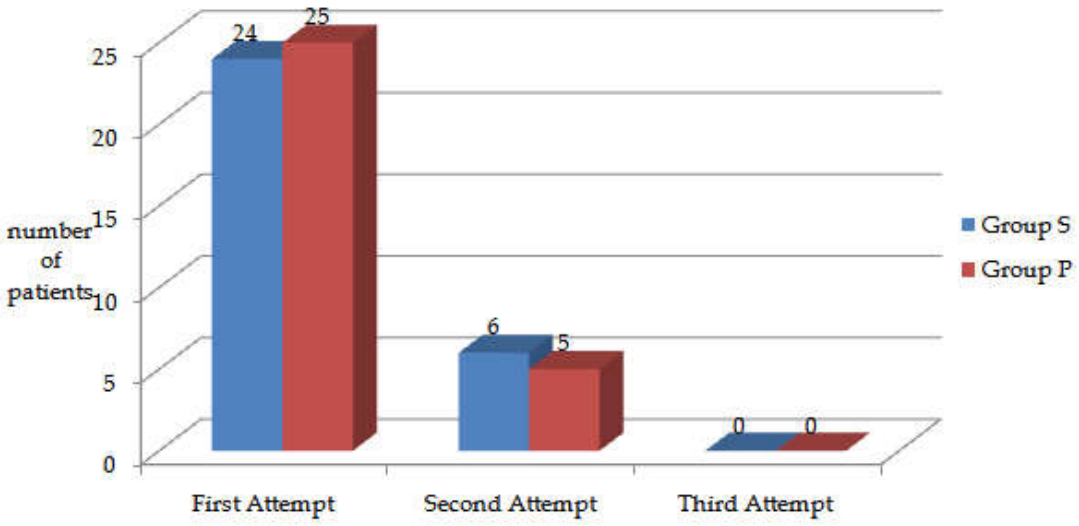
CHI – 0.21, DF = 1, P=0.64

Tables 1 and 2 shows 28 of 30 insertions in group LMA-S were in the first attempt and only 2 patient required 2nd attempt. 27 of 30 in the group LMA-P required only one attempt and 3 patients required 2nd attempt. The attempt of insertion was not statistically significant between the two groups (p>0.05).

Table 3: Showing insertion time

Group	Group S	Group P	P value	T value
Time in sec (mean duration)	15.90±2.52	17.80±1.69	0.001	3.4

Table 3 shows the mean duration of insertion of LMA-S and LMA-P in patients were 15.90±2.52 and 17.80±1.69 seconds respectively and was statistically significant (p<0.05).



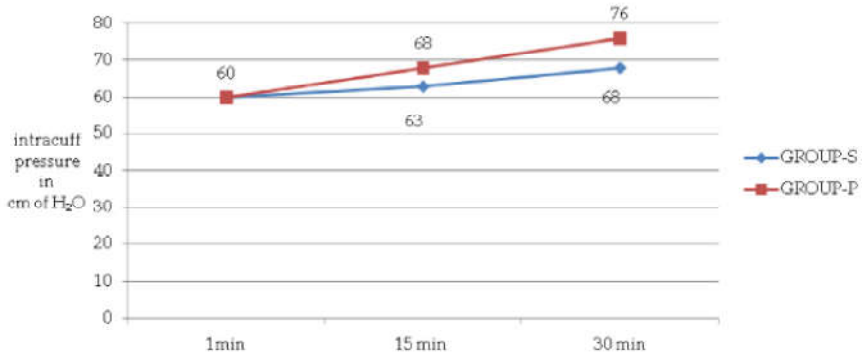
Graph 1: Showing ease of passing ryles tube

Graph 1 shows ease of passing ryles tube in group LMA-S in 24 patients it was passed in first attempt and 6 patients in second attempt. In group LMA-P in 25 patients it was passed in first attempt and 5 patients in second attempt, there was no statistical significant difference between two groups (p>0.05)

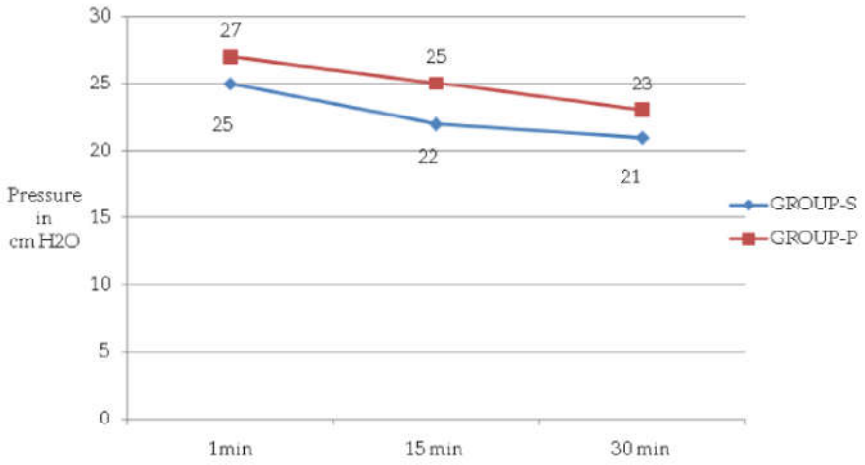
Graph 2 showing intracuff pressure in cm H_2O at time intervals 1 min, 15 min and 30 min. In group LMA-S it was 60, 63 and 68 respectively and in group LMA-P it was 60, 68 and 76 respectively. There was statistical significant difference between two groups at 15 and 30 min (p<0.05).

Graph 3 showing oropharyngeal leak pressure in cm of H_2O in both groups at 1 min, 15 min and 30 min. In group LMA-S it was 25.27±1.20, 22.83±1.34, 21.17±0.95 respectively and in group LMA-P it was 27.50±1.28, 25.67±1.58, 23.23±1.13. There was statistical significance at 1 min, 15 min and 30 min (p<0.05).

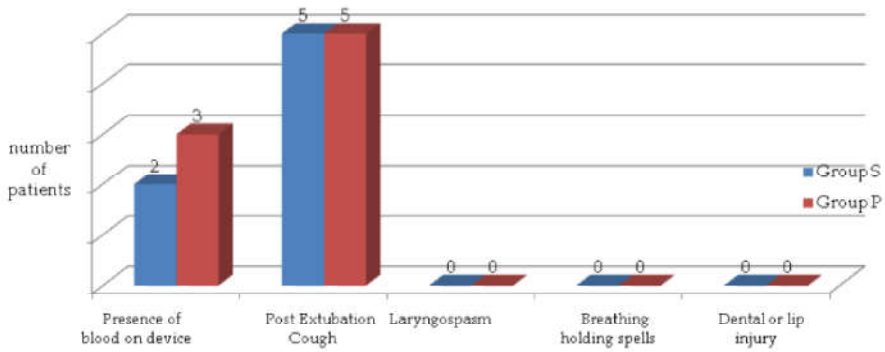
Graph shows 5 patients in both the groups had post extubation cough and 2 patients in LMA-S group and 3 patients LMA-P group had blood tinged LMA after removal.



Graph 2: showing intracuff pressure at respective intervals



Graph 3: Showing Oropharyngeal leak pressure at respective time intervals



Graph 4: Showing complication

Discussion

The major responsibility of the anesthesiologist is to provide adequate ventilation to the patient. The most vital element in providing respiration is maintenance of patent airway. The tracheal intubation is the gold standard method for maintaining a patent airway during anaesthesia [9].

The supraglottic airway device is a novel device that fills the gap in airway management between tracheal intubation and use of face mask [10].

Proseal laryngeal mask airway has a dorsal cuff, in addition to the peripheral cuff of LMA, which pushes the mask anterior to provide a better seal around the glottic aperture [7]. The new LMA supreme is a latex free laryngeal mask airway, made of medical grade PVC. The firm, elliptical and anatomically shaped airway tube facilitates easy insertion [8].

There are many literature comparing both these devices with contradictory results.

Thus, this study was designed to compare the clinical efficacy of LMA-P airway and LMA-S to evaluate insertion attempts, oropharyngeal leak pressure, duration of insertion, ease of passing ryles tube, intracuff pressure and any complications in patients undergoing elective surgeries under general anaesthesia.

A total of 60 ASA grade I-II patients aged 18-60 who were scheduled for surgery under general anaesthesia were randomized into two groups 30 in each and enrolled in our study.

Age incidences between two groups were comparable. Most of the patient's age in both the groups ranged from 21-30 yrs. The difference between two mean ages are not statistically significant.

The male to female ratio in LMA-S group is 12/18 and in LMA-P group is 14/16. There is no statistical difference between the groups.

In our study both the device insertions were easy and there were no failure. In LMA-S group it was inserted in first attempt in 28 patients and in second attempt in rest 2. In LMA-P group it was inserted in first attempt in 27 patients and in second attempt in rest 3. This is similar to the study conducted by Hosten T, et al. [11] who conducted study comparing LMA-S and LMA-P in 60 patients where there was no difference in insertion attempts.

Study conducted by Belena JM, et al. [12] showed success rate of the first attempt insertion was higher in LMA-S group, this difference might be due to not usage of muscle relaxant in this study while inserting LMA.

Time required for insertion in LMA-S group and LMA-P group was 15.90±2.52 sec and 17.80±1.69 sec respectively. Time required for LMA-S was less compared to LMA-P and it showed statistical significance ($p=0.001$). Study done by Hosten T et al. [11] and Belena JM, et al. [12] showed no difference in both groups in time taken for inserting the device. Clinically this difference what we observed has no significance.

Ease of passing ryle's tube was similar in both groups, with success rate of group LMA-S in 24 patients it was passed in first attempt and 6 patients in second attempt. In group LMA-P in 25 patients it was passed in first attempt and 5 patients in second attempt, there was no statistical difference between two groups ($p=0.73$). Belena JM, et al. [12] had got similar results but study done by Hosten T et al. [11] showed failure of passing ryles tube in 5 patients in LMA-P group. The drainage tube of S-LMA is directly posterior to the ventilatory side and travels strictly midline and opens at the distal end of the cuff. We believe that an improved drainage tube design may explain the improved success rate of ryle's tube passage in LMA-S. It depends on the amount of jelly used and size in our study we made sure we used adequate jelly for passage and the appropriate size this might be the reason of no failures in our study.

In our study we measured intracuff pressure in cm of H_2O at 1 min, 15 min and 30 min interval in both groups LMA-S and LMA-P it was 60, 63.43±1.10, 68.37±1.32 and 60, 68.37±1.32, 76.87±2.6 respectively, It was observed that as the time elapsed the intracuff pressure increased in group LMA-P ($p<0.05$), similar result was seen in study conducted byHosten T et al. [11] where they measured ICP at 30 and 60 min interval.

The increase in the intracuff pressure in LMA-P group can be explained in the sense that LMA-S is constructed from polyvinyl chloride in contrast to LMA-P, which is constructed from silicon. The cuff of the LMA-P is highly permeable to N_2O and ICP increase during N_2O anesthesia.

In a study conducted by Keller C, et al. [13] they observed the effect of ICP on OLP and fibreoptic position with LMA, they concluded that LMA functions better at sub-maximal cuff volumes.

By observing this it is very necessary to measure and adjust the ICP at time intervals by the help of hand held pressure gauge.

Owing to the moderate pharyngeal seal provided

by the supraglottic airway devices, controlled ventilation may not be always possible and there is a risk of pulmonary aspiration of regurgitant matter. Aspiration requires regurgitant fluid to reach the laryngeal inlet and it depends on the seal the SAD makes with oesophagus (oesophageal seal) combined with seal with pharynx (pharyngeal seal), which will determine the likelihood of spill into the larynx [14].

In our study we measured OLP in cm of H_2O at 1 min, 15 min and 30 min time interval in both groups LMA-S and LMA-P it was 25.27±1.20, 22.83±1.34, 21.17±0.95 and 27.50±1.28 25.67±1.58, 23.23±1.13 respectively it is seen that all time intervals group LMA-P had high OLP compared to the group LMA-S ($p<0.05$).

Similar result was found in study done by Balena JM et al. [12] where they compared LMA Proseal and LMA Supreme among 120 adult patients. They observed mean oropharyngeal leak pressure in the LMA Proseal group was significantly higher than that in the LMA Supreme group (30.7±6.2 versus 26.2±4.1 cm H_2O; $P<0.01$). Lee et al. [15] observed The mean oropharyngeal leak pressure in the LMAS was significantly lower than in the PLMA (27.9±4.7 vs 31.7±6.3 cm H_2O, $P = 0.007$).

Hosten T et al. [11] conducted similar study in 60 adult patients they observed Oropharyngeal leak pressures were similar (LMA Proseal: 26.9±6.6 cm of H_2O; LMA Supreme: 26.1±5.2 cm of H_2O). This study showed no differences in OLP between devices, although it only included female patients with a size 4 LMA.

Verghese C et al. [16] comparing LMA-P and LMA-S in 36 patients showed no difference in the OLP. In only 22 were given muscle relaxant so this might have had an effect on OLP.

The higher OLP for the LMA-P is mainly related to the dorsal cuff and the silicone rubber double cuff design compared to the polyvinyl chloride single cuff of the LMA-S. Lower OLP observed in LMA-S may be due to the movement of the semi-rigid curved airway tube, something which doesnot seem to happen with the elastic tube of the LMA-P.

In our study no patient had serious complication, 5 patients in both the group had post Extubation cough and 2 patients in LMA-S group and 3 patients LMA-P group had blood tinged LMA after removal.

Study conducted by Balena JM et al. [12] observed sore throat in both groups 17 and 21 had in group LMA-S and LMA-P respectively and no patients suffered from any serious complication.

Hosten T et al. [11] also showed no difference between two groups in intraoperative and post operative complication rate.

There are limitations to our study. First, insertions were done in patients with normal airway (MPC grade I, II) and normotensive patients. Present results may not apply to patients with difficult airways and hypertensive patients. Second, present results are specific to the anesthetic administered and might not apply for other anesthesia regimes. there was no blinding in the data collection, which is a possible source of bias.

Thus, the results of these various studies comparing the efficacy of the LMA-S and LMA -P shows both devices are similar in terms of insertion attempts, ease of passing ryles tube and complication rate. Insertion time required to insert LMA-S is less compared to LMA-P. Intracuff pressure increased more quickly in LMA-P compared to LMA-S. Oropharngeal leak pressure was better in LMA-P group compared to LMA-S group.

Conclusion

Both LMA Supreme and LMA Proseal can be used safely and effectively in selected patients undergoing general anaesthesia. LMA supreme is easy to insert compared to LMA Proseal but LMA Proseal had better oropharyngeal seal compared to LMA Supremeinspite of increased intracuff pressure. Ease of passing ryles tube was similar in both groups, complication of usage of LMA are minimal and similar in both the devices.

References

1. Sharma B, Sahani C, Bhattacharya A, Kumar VP, Sood J. Proseal laryngeal mask airway: A study of 100 consecutive cases of laproscopic surgery, Indian J Anaesth. 2003;47:467-72.
2. Gupta S, Sharma R, Jain D. Airway assessment: Predictors of difficult airway. Indian J Anaesth. 2005; 49(4):257-62.
3. Gal TJ. Airway management. In: Miller RD, editor. Textbook of anaesthesia, 6th ed. Philadelphia: Elsevier; 2005.pp.1617-52.
4. Jayashree S. Laryngeal mask airway and its variants. Indian J Anaesth. 2005;49:275-80.
5. Helmy AM, Atef HM, El-Taher EM, Henidak AM. Comparative study between i-gel, a new supraglottic airway device, and classical laryngeal mask airway in anesthetized spontaneously ventilated patients. Saudi J Anaesth. 2010;4(3):131-6.

6. Keller C, Brimacombe J, Bittersohl J, Lirk P, Goedecke A. Aspiration and the laryngeal mask airway: three cases and a review of the literature. British Journal of Anaesthesia. 2004;93(4):579-82.
7. Misra MN, Ramamurthy B. The pro-seal LMAtm and tracheal tube: A comparison of events at insertion of the airway device. Internet J Anesthesiol 2007;16(2).
8. Abdi W, Amathieu R, Adhoum A, Poncelet C, Slavov, et al. Sparing of larynx during gynaecological laproscopy: a randomized trial comparing the LMA Supreme and the ETT. Acta Anaesthsio Scand. 2010; 54(2):141-6.
9. The European Resuscitation Council (ERC) and the American Heart Association (AHA) in collaboration with the International Liaison Committee on Resuscitation (ILCOR): International Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiac Care. An International Consensus on Science. Resuscitation. 2000;6:29-71.
10. Pennant JH, White PF. The laryngeal mask airway its uses in anaesthesiology. Anesthesiology. 1993 Jul;79(1):144-63.
11. Hosten T, Gurkan Y, Ozdamar D, Tekin M, Toker, Solak M. A new supraglottic airway device: LMA-supreme, comparison with LMA-proseal. Acta Anaesthesiol Scand. 2009;53(7):852-7.
12. Belena JM, Nunez M, Anta D, Carnero M, Gracia JL, Ayala JL et al. Comparison of Laryngeal mask airway Supreme and Laryngeal mask airway Proseal with respect to oropharyngeal leak pressure during laproscopic cholecystectomy: a randomized controlled trial. Eur J Anaesthesiol. 2013 Mar; 30(3):119-23.
13. Keller C, Brimacombe JR, Morris R. Comparison of four methods for assessing airway sealing pressure with laryngeal mask airway in adult patients. Br J Anaesth. 1999;82:286-87.
14. Woodall N, Cook TM. A national census of airway management techniques employed during anaesthesia in the UK: results of the first phase of the 4th National Audit Project at the Royal College of Anaesthetists. Br J Anaesth. 2011 Feb;106(2):266-71.
15. Lee AK, Tey JB, Lim Y, Sia AT. Comparison of the single-use LMA Supremewith the reusable Proseal LMA for anaesthesia in gynaecological laparoscopic surgery. Anaesth Intensive Care. 2009;37:815–19.
16. Verghese C, Ramaswamy B. LMA-Supreme TM a new single use LMA TM with gastric access: a report on its clinical efficacy. Br J Anaesth. 2008; 101(3):405-10.

Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(1) (Part - II): 197-205
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.28

To Study and Compare Efficacy of Ropivacaine and Bupivacaine for Caudal Analgesia in Paediatric Patients

Aishwarya Bandewar[1], Alok Kumar[2], Manish Kokne[3]

[1]Assistant Professor [2]Junior Resident, Department of Anaesthesia, MGM Medical College, Kamothe, Navi Mumbai, Maharashtra 410209, India, [3]Assistant Professor, Department of Pharmacology, HBT Medical College, Mumbai, Maharashtra 400056, India.

Abstract

Aims and objectives: The aim of the study was to compare quality and duration of intra and post operative analgesia and need of rescue analgesia of 0.5 ml/kg of 0.25% Bupivacaine. and 0.5 ml/kg of 0.2% Ropivacaine. *Methodology:* We conducted a prospective, randomized, double blind study, in which 60 paediatric patients undergoing lower abdominal and genitourinary surgeries. Group A received 0.5 ml/kg of 0.25% Bupivacaine and Group B received 0.5 ml/kg of 0.2% Ropivacaine. Quality and duration of motor block, Adjunct to general anaesthesia, Margin of safety of ropivacaine over Bupivacaine was assessed. *Results:* Both the drugs provided post-operative analgesiaMean duration of post-operative analgesia is 344.5±29.37 min in group A & that In group B is 346.3±10.66 min (paired) two tailed p value is 0.749 which is comparable & statistically not significant. Mean duration of motor block in group A is 176.6±21.02 min and in group B was 103.8±11.79 min with P value of 0.0001 which is statistically significant. The incidence of the side effect between the two groups is not statistically significant. *Conclusion:* Caudal block with 0.2% Ropivacaine resulted in equal duration of analgesia with less duration of motor block as compared with 0.25% caudal Bupivacaine, without an increase in incidence of side effects when administered pre-operatively in a volume of 0.5 ml/kg to children undergoing lower abdominal and urogenital surgeries.

Keywords: Ropivacaine; Bupivacaine; Abdominal and urogenital surgeries.

How to cite this article:

Aishwarya Bandewar, Alok Kumar, Manish Kokne. To Study and Compare Efficacy of Ropivacaine and Bupivacaine for Caudal Analgesia in Paediatric Patients. Indian J Anesth Analg. 2019;6(1):197-205.

Introduction

Pain is by far one of the most common and distressing effects of disease and all medical persons regard its relief as one of their main duties. An acute pain service must act as a research vehicle while anaesthesiologists remain crucial contributors in the fascinating field of pain management. If pain is agony, relieving pain is ecstasy. "Failure to relieve pain is morally and ethically unacceptable". Adequate pain relief is considered as basic human right. Whether it is by drug, nerve injection, surgery or any other means, every patient want desperately to be relieved by pain. The history of pain management in children is rather described as under diagnosis, misinterpretated. It was misbelieved that children do not suffer from the pain they don't feel it, they

Corresponding Author: Manish Kokne, Assistant Professor, Department of Pharmacology, HBT Medical College, Mumbai, Maharashtra 400056, India.

E-mail: manishkkn1120@gmail.com

Received on 11.01.2019, **Accepted on** 02.02.2019

tolerate the discomfort well, they don't respond to the pain as adult do. Therefore paediatric pain management is challenging and one of the frontiers of modern anaesthesiology.

The post-operative pain has equal importance as that of operative analgesia, Relief of post-operative pain is a challenge for all anaesthesiologists. Expressions of gratitude from patients, free of pain can contribute to feelings of self-esteem and job satisfaction.

In the last 15 years, the use of innovative techniques for the management pain, the awareness of severe complications connected with insufficient pain relief, the neurohormonalsequelae connected with pain, created new philosophy due to which at present there is no reason why neonates, infants and children should be denied of adequate analgesia.

There are many reasons for surgical encounter of the little-angels in the early childhood, lower abdominal surgeries being the most common. They are associated with considerable post operative pain which results in restlessness, agitation, bleeding and psychological stress in children. Insufficient pain relief in early post-operative period also leads to delay in full recovery, prolonged hospital stay, discouraged ambulation, behavioural and psychological problems and parental agony. Caudal epidural block being prescribed by many as the "Wonder Technique" for analgesia has a definitive place in the post-operative pain relief protocols in many hospitals. Caudal epidural block is the most commonly used regional technique for post-operative analgesia in children.

In order to maximize post-operative analgesia, a number of agents been tried by epidural and spinal route. Epidural and spinal opioids have been used but the associated major side effects like sedation; itching, urinary retention, nausea, and vomiting, respiratory depression have limited widespread use. Ropivacaine which is newer and long-acting amide local anaesthetic with a potentially improved safety profile when compared to bupivacaine [1,2]. Ropivacaine being less lipophilic, it is less likely to penetrate in large myelinated motor fibres as compared to bupivacaine, resulting in a relatively earlier recovery from motor blockade without compromising duration of sensory blockade. This property of ropivacaine is helpful in earlier diagnosis of nerve injury which can occur during reduction and fixation of upper limb fractures. Ropivacaine has selective action on the pain-transmitting Aδ and C nerves rather than Aβ fibres, which are involved in motor function. Many comparative studies between ropivacaine and bupivacaine proved that ropivacaine produces less cardiac as well as central nervous system toxic effects, less motor block and a similar duration of action of sensory analgesia as bupivacaine [3,4].

Because of the side effects of bupivacaine which include motor weakness, cardiovascular and central nervous system toxicity, this study was conducted to compare duration of analgesia, motor block, incidence of side effects with single shot caudal block with either 0.2% Ropivacaine or 0.25% Bupivacaine.

Aims and Objectives

1. To compare quality and duration of intra and post operative analgesia and need of rescue analgesia
2. To compare quality and duration of motor block
3. As an adjunct to general anaesthesia
4. To compare margin of safety of ropivacaine over Bupivacaine.

Material and Methods

The present randomized prospective study titled "To study and compare efficacy of Ropivacaine and Bupivacaine for caudal analgesia in paediatric patients." was carried out; after obtaining the local ethical committee approval. 60 patients of either sex requiring GA with Caudal block for lower abdominal surgeries and genitourinary surgeries were selected after fulfilling following inclusion and exclusion criteria. Patient of ASA class I between 1 year to 10 years of age Patient of both sexes undergoing only elective lower abdominal surgery, genitourinary surgeries were included in the study.

Patients with neurological diseases, bleeding disorders, local infection at the site and patients with obvious skeletal deformities were excluded from the study and patients with upper respiratory tract infections, cardiorespiratory diseases, systemic Problems, meningocele and myelocelewere excluded.

Each patient was examined and interviewed (parents also) on the evening prior to operation. Detailed history about previous illness and treatment was elicited. Thorough physical examination was carried out and patients weight was recorded. Investigations like haemoglobin estimation, urine analysis for albumin and sugar, TLC and DLC were done.

All the parents were informed regarding the procedures of anaesthesia and surgery and a written consent of the parents was obtained.

The children were kept nil by mouth for atleast 4 hours before surgery and mothers were informed to give glucose water in the morning 4 hours before the scheduled time of surgery. Oral Midazolam 0.5 mg/kg 30 minutes before scheduled time of surgery was given.

After taking patient on operating table, the standard intra operative monitors i.e. ECG, NIBP, pulse oximeter & temperature probe were applied. Intravenous cannulation was done with 22G or 24G cannula and crystalloid (ringer lactate)infusion was started according to Holiday Segar formula.

Preoxygenation with 100% oxygen by mask was done for 3 minutes. Premedication was done with iv inj. Glycopyrrolate (0.004 mg/kg), inj. Ondensetron (0.08 mg/kg) excluding opioid analgesics. Anaesthesia was induced with injpropofol (2 mg/kg) iv & inj atracurium (0.5 mg/kg) iv was given after checking mask ventilation. Endo tracheal intubation was performed after 3 minutes. Anaesthesia was maintained with O_2 + N_2O + isoflurane through Jackson-Rees paediatric circuit with controlled ventilation.

Then the child was placed in the lateral position with the hips and knees flexed and caudal block was performed. The sacral region was prepared with betadine and spirit solution and following identification of sacral cornua, a 23G needle was inserted into the skin overlying the sacral hiatus. The epidural space was identified by the loss of resistance when the needle pierced the sacrococcygeal ligament. The needle was made parallel to the back and inserted into the canal 2-3 mm more. After the negative aspiration for blood or CSF, the drug was injected.

Group A – 0.5 ml/kg of 0.25% Bupivacaine

Group B – 0.5 ml/kg of 0.2% Ropivacaine

Continuous ECG, B.P, heart rate, pulseoximetric measurements were recorded. After the block (any of the two), patients were placed in supine position and Surgery was carried out. anaesthesia was maintained with oxygen (40%), nitrous oxide (60%), Isoflurane (1-1.5%) and top ups of muscle relaxant. Heart rate (ECG), NIBP & oxygen saturation (SpO_2) was monitored intraoperatively for every 5 mins for first 15 minutes & thereafter every 15 mins till the end of surgery. At the end of surgery, residual neuromuscular blockade was reversed with iv inj. Neostigmine (0.05 mg/kg) & Glycopyrrolate (0.008 mg /kg) & Thorough oropharyngeal and endotracheal suction was done and patient was extubated after return of reflexes.

Post operatively Heart rate, NIBP & oxygen saturation (SpO_2), pain score & motor blockade was monitored at 15 min, 30 min, 60 min, 90 min, 120 min, 3 hr, 4 hr, 5 hr, 6 hr after surgery. Pain was assessed by mCHEOPS score. Inj paracetamol 20 mg/kg wasgiven iv when mCHEOPS score was greater than 4. The time from caudal block to first post op rescue analgesic administration was the end point of study. Finally assessment of the duration of effective analgesia was done by comparing time from caudal block to administration of first analgesic. Degree of motor blockade was assessed by motor power scale. Other adverse effects like nausea, vomiting, facial flushing, fever were noted. Both groups were comparable in respect to mean age, sex, weight and duration of surgery.

Results

Both groups were comparable in respect to mean age, sex, weight and duration of surgery. The mean duration of surgery in group Ais 58±21.51 min. and of group (B) is 53.33±16.78 min. The difference is not statistically significant. Mean total duration of surgery is more or less same in both the groups.

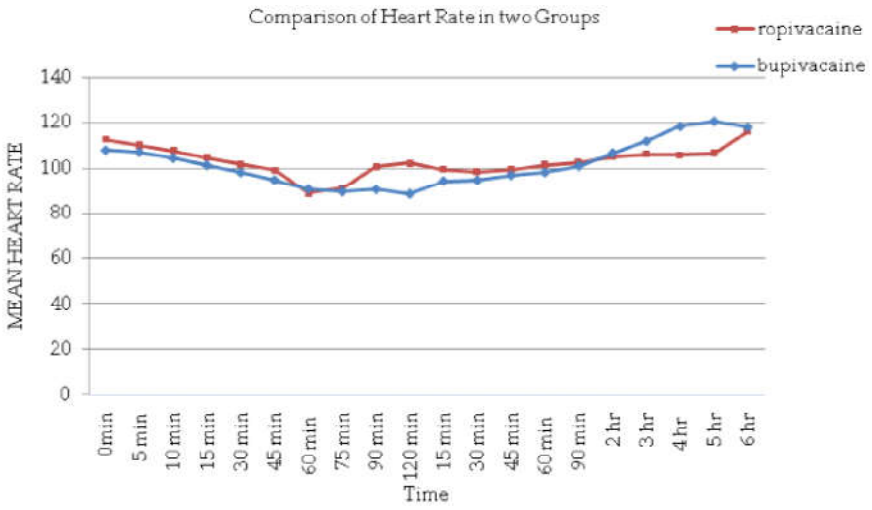
In this study group the mean pulse rate in group A is 107.77±13.942 /min, in group B is 112.67±16.647/min in preoperative period, this is comparable. The difference is not statistically significant. The pulse rate remained stable throughout intra operative period in both the groups. In post operative period, pulse rate remained stable up to 2 hours in both group A and group B. There is slight increase in pulse rate seen after 3 hours post operativein group A, while in group B it is stable (Table 1).

In this the mean preoperative systolic blood pressureis 103.13±6.532 mm of Hg ingroup A and in group B is 101.87±6.033 mm of Hg which is comparable and the difference is not statistically significant. The systolic blood pressure remained stable and comparable in both the groups throughout the intra operative period. In post operative period, systolic blood pressure remained stable up to 2 hours in both group A and group B. There is slight increase in systolic blood pressure seen after 3 hours post operative in group A, while in group B it is stable (Table 2).

In this the mean preoperative diastolic blood pressure is 53.8±4.881 mm of Hg ingroup A and in group B is 54.4±6.134 mm of Hg which is comparable and the difference is not statistically significant.

Table 1: Comparison of Changes in the Pulse Rate in two Groups

Mean		Bupivacaine A		Ropivacaine B		P value	Significance
		Std. Deviation	Mean	Std. Deviation	Mean		
Pre-op	0 min	107.77	13.942	112.67	16.647	0.221	Not significant
Intra-op	5 min	106.93	13.196	109.77	16.644	0.468	Not significant
	10 min	104.33	12.704	107.23	15.456	0.43	Not significant
	15 min	101.27	12.889	104.47	15.793	0.393	Not significant
	30 min	98.07	14.263	101.57	15.776	0.371	Not significant
	45 min	94.76	13.185	99.17	16	0.254	Not significant
	60 min	90.65	12	88.88	11.057	0.663	Not significant
	75 min	89.63	10.849	90.75	11.354	0.871	Not significant
	90 min	90.4	12.522	100.5	2.121	0.332	Not significant
	120 min	88.5	14.849	102	2.3	0.593	Not significant
Post-op	15 min	94.27	11.753	99.2	15.314	0.167	Not significant
	30 min	94.67	10.466	98.23	13.733	0.263	Not significant
	45 min	96.83	9.502	99.37	14.308	0.422	Not significant
	60 min	98	8.781	101.27	13.235	0.265	Not significant
	90 min	100.97	7.289	102.4	13.014	0.601	Not significant
	2 hour	106.5	7.291	104.87	13.994	0.573	Not significant
	3 hour	111.83	6.783	105.93	14.125	0.044	Significant
	4 hour	118.4	7.546	105.6	14.265	0.01	Significant
	5 hour	120.68	8.41	106.32	13.94	0.01	Significant

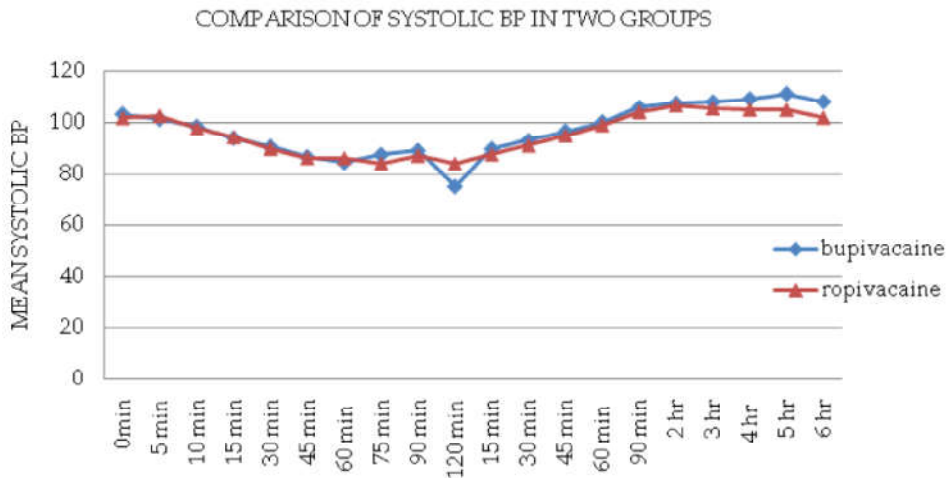


Graph 1:

Table 2: Comparison of Changes in the Systolic B.P.

Mean		Bupivacaine A		Ropivacaine B		P value	Significance
		Std. Deviation	Mean	Std. Deviation	Mean		
Pre-op	0 min	103.13	6.532	101.87	6.033	0.438	Not Significant
Intra-op	5 min	101.2	5.448	102.73	6.528	0.327	Not Significant
	10 min	98.33	6.83	97.8	7.034	0.767	Not Significant
	15 min	93.87	8.565	94.33	7.862	0.827	Not Significant
	30 min	90.33	7.915	89.87	8.959	0.831	Not Significant
	45 min	86.48	7.609	86.27	9.032	0.921	Not Significant
	60 min	84.35	6.901	86.13	8.747	0.522	Not Significant
	75 min	87.25	9.794	84	4.899	0.552	Not Significant
	90 min	88.8	13.084	87	4.243	0.863	Not Significant
	120 min	75	4.243	84	.4.63	0.333	Not Significant

Post-op	15 min	89.53	6.383	87.53	7.838	0.283	Not Significant
	30 min	92.87	5.649	91	7.423	0.278	Not Significant
	45 min	96.41	5.11	95.07	6.028	0.359	Not Significant
	60 min	100.07	4.441	99.13	4.918	0.444	Not Significant
	90 min	105.73	3.269	104.2	3.295	0.076	Not Significant
	2 hour	107.33	2.591	106.73	2.377	0.354	Not Significant
	3 hour	107.93	3.503	105.67	5.228	0.053	Significant
	4 hour	109.13	5.002	105.2	4.221	0.002	Significant
	5 hour	111.12	4.729	105.14	3.979	0.001	Significant



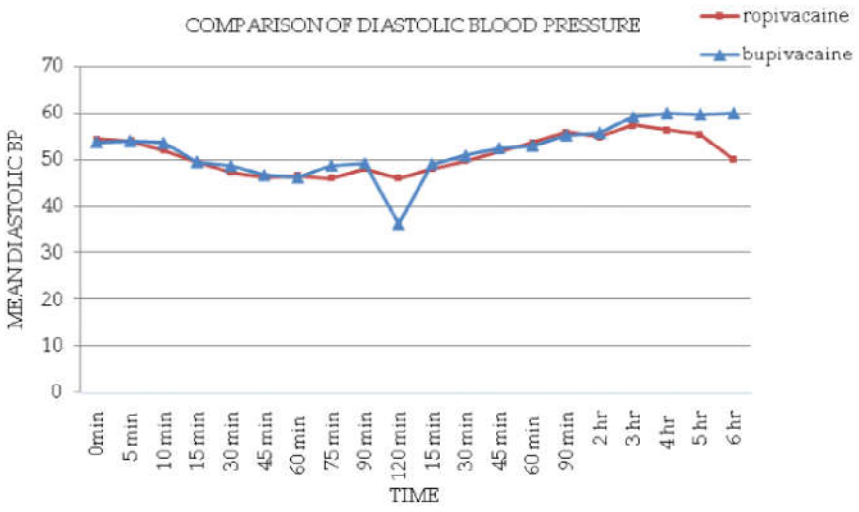
Graph 2:

Table 3: Comparison of Changes in the Diastolic B.P.

Mean		Bupivacaine A		Ropivacaine B		P value	Significance
		Std. Deviation	Mean	Std. Deviation	Mean		
Pre-op	0 min	53.8	4.881	54.4	6.134	0.677	Not Significant
Intra-op	5 min	54.07	3.463	54.07	5.078	1	Not Significant
	10 min	53.6	4.994	52.07	4.712	0.226	Not Significant
	15 min	49.53	5.164	49.4	5.308	0.922	Not Significant
	30 min	48.6	6.871	47.2	5.671	0.393	Not Significant
	45 min	46.69	6.217	46.2	6.088	0.761	Not Significant
	60 min	46.12	4.029	46.63	5.965	0.775	Not Significant
	75 min	48.75	5.849	45	5.774	0.318	Not Significant
	90 min	49.2	9.121	48	2.828	0.869	Not Significant
	120 min	36	5.657	46	2.57	0.386	Not Significant
Post-op	15 min	49.07	5.552	47.93	6.528	0.472	Not Significant
	30 min	50.87	5.77	49.87	6.516	0.532	Not Significant
	45 min	52.53	4.953	51.87	6.642	0.661	Not Significant
	60 min	53	5.401	53.6	4.082	0.629	Not Significant
	90 min	55.33	4.678	55.87	5.198	0.678	Not Significant
	2 hour	55.87	4.297	54.93	5.959	0.489	Not Significant
	3 hour	59.2	4.597	57.47	4.783	0.158	Not Significant
	4 hour	60.07	6.443	56.47	5.244	0.021	Significant
	5 hour	59.84	6.656	55.36	4.961	0.007	Significant

The diastolic blood pressure remained stable and comparable in both the groups throughout the intra operative period. In post operative period, diastolic blood pressure remained stable up to 3 hours in both group A and group B. There is slight increase in diastolic blood pressure seen after 4 hours post operative in group A, while in group B it is stable (Table 3).

Mean pain score in both groups are more or less same up to 2 hours, and the difference is statistically not significant. After this, in 3rd and 4th post operative period mean pain score in group A ismore than mean pain score in group B, and the difference is statistically significant. In 5 thpost operative hour, most of the patients in both groups required rescue analgesia (Table 4).



Graph 3:

Table 4: Comparision of Changes in Pain Score

Mean		Bupivacaine A		Ropivacaine B		P value	Significance
		Std. Deviation	Mean	Std. Deviation	Mean		
Post-op	15 min	0	0	0.03	0.183	0.321	Not Significant
	30 min	0.2	0.407	0.17	0.461	0.768	Not Significant
	45 min	0.93	0.254	1.03	0.32	0.185	Not Significant
	60 min	1.13	0.346	1.17	0.379	0.723	Not Significant
	90 min	1.73	0.45	1.63	0.49	0.414	Not Significant
	2 hour	2.07	0.254	2.1	0.305	0.647	Not Significant
	3 hour	2.67	0.479	2.13	0.346	0	Significant
	4 hour	3.17	0.379	2.8	0.551	0.004	Significant
	5 hour	3.96	0.2	3.96	0.189	0.936	Not Significant

Graph 4:

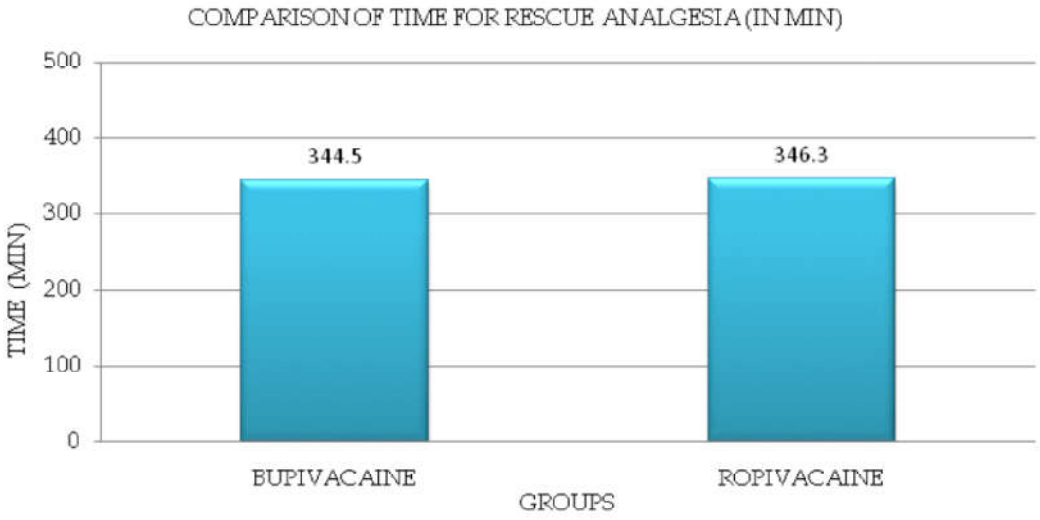
Mean time for rescue analgesia between two groups is statistically not significant (Table 5).

Mean duration of motor block in group A is 176.6 ±21.02 min and in group B is 103.8±11.79 min with p value of 0.000 which is statistically significant.

In group A, side effects are seen in 5 out of 30 patients (Flushing =2, Nausea vomiting= 3) In group B, side effects are seen in 5 out of 30 patients (Flushing = 3, Nausea vomiting= 2). p value is 1 and the difference is statistically not significant (Table 6).

Table 5: Comparison of Time for Rescue Analgesia

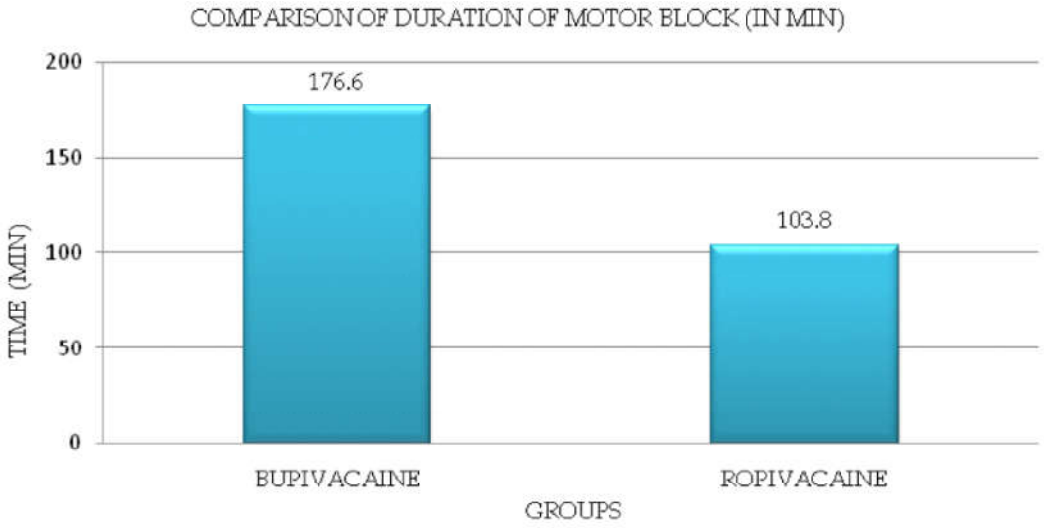
	Group	N	Mean	Std. Deviation	Std. Error Mean	P value	Significance
DOA	Bupivacaine A	30	344.5	29.37	5.36	0.749	Not Significant
	Ropivacaine B	30	346.3	10.66	1.94		



Graph 5:

Table 6: Comparison of Duration of Motor Block

	Group	N	Mean	Std. Deviation	Std. Error Mean	P value	Significance
DOMB	Bupivacaine A	30	176.6	21.02	3.83	0.000	Significant
	Ropivacaine B	30	103.8	11.79	2.15		



Graph 5:

Discussion

Post-operative pain is an acute pain, which starts with surgical trauma and usually ends with tissue healing. Post-operative analgesia has been neglected for a long time whereas post-operative pain has been considered an inevitable cost of operations. Post-operative pain, apart from causing discomfort and distress, has got deleterious effects on body mechanisms.

The caudal block is most accepted method of analgesia in children undergoing inguino-genital operations, used for providing both surgical and postoperative analgesia. Caudal epidural block, advocated by Kay B (1974) [5] using 0.5% bupivacaine with 1 : 200000 Adrenaline at dose rate of 0.5 ml/year of age is an effective and simple method. They proposed that the identification of the landmarks of the blocks i.e. sacrococcygeal hiatus is extremely easy in children and block application is rapid and easy with minimal failure. It requires lateral or prone positioning. This block has produced satisfactory operative anaesthesia and post-operative analgesia.

Trend of changes in the pulse rate-

In this study group the mean pulse rate in group A is 107.77±13.942 /min, in group Bis 112.67±16.647/min. the pulse rate remained stable throughout intraoperative period in both the groups. In post-operative period pulse rate remained stable up to 2 hours in both groups. There is slight increase in pulse rate seen after 3 hours post operative in group A while in group B it is stable. This time correlate with the time when mean pain score in group A is more than that in group B, leading to increase in the pulse rate and group B did not have pain at this time leading to stable pulse rate. This finding correlated well with the study performed by Conceicao et al., (1998) [6]. Similarly in the study conducted by Rosemary Hickey et al (1991) [7] did not observe at significant variation in the mean pulse rate and systolic blood pressure between 0.5% ropivacaine and 0.5% bupivacaine at different time intervals.

Trend of changes in the blood pressure-

In this study mean preoperative blood pressure both systolic and diastolic is comparable and the difference is not statistically significant. Blood pressure remained stable and comparable in both the groups throughout the intraoperative period .But in the postoperative period the BP showed slight increase in group A with statistically significant difference. Similarly as the patient had tachycardia they also showed increase in the blood pressure due to pain. This finding correlated well with the study performed by Conceicao et al., (1998) [6]. Similarly in the study conducted by Rosemary Hickey et al. (1991)[7] did not observe at significant variation in the mean systolic blood pressure between 0.5% ropivacaine and 0.5% bupivacaine at different time intervals.

Trend of changes in pain score-

In this study mean pain score in both groups are more or less similar up to 2 hours post operative. The difference is statistically not significant. After this in 3rd & 4th post operative period mean pain score in group A is 2.670.479 and 3.170.379, while in group B is 2.130.346 and 2.80.551 respectively. The difference is statistically significant. In 5th post operative hour, most of the patients in both groups required rescue analgesia. This finding correlated well with the study performed by Conceicao et al., (1998) [6].

Comparison of duration of analgesia-

The duration of adequate post-operative analgesia or pain free period was taken as time from caudal analgesic till the pain score ≥ 4 was observed at which time rescue analgesic was given. In group A the mean duration of analgesia is 344.5 ±29.37 min while that in group B is 346.3±10.66 min. (paired) two tailed p value 0.749 which is statistically not significant. The mean duration of post-operative pain relief (or pair free period) between the two groups is not significant. This finding correlated well with the study performed by Conceicao et al., (1998) [6]. Studied done by Hickey R, Candido (1990) [7], Casati A, Fanelli G (1999) [8] also showed duration of analgesia with ropivacaine was 11-14 hrs while with bupivacaine it was 10-12 hrs which was not statistically significant.

Comparison of duration of motor block-

Mean duration of motor block in group A is 176.6 ±21.02 min and in group B is 103.8±11.79 min with P value of 0.000 which is statistically significant. This finding correlated well with the study performed by Conceicao et al., (1998) [6]. Similarly in the study conducted by Surendra Raikwar et al., Onset of sensory & motor blockade was 12.9±2.8 minutes and 13.2±1.99 minutes in Ropivacaine and for bupivacaine it was 15.9±2.8 minutes and 20.2± 3.22 minutes which was found to be significant for group R ($p<0.05$) [9].

Comparison of side effects-

In group A, side effects are seen in 5 out of 30 patients. In group B, side effects are seen in 5 out of 30 patients p value is 1 and the difference is statistically not significant. This finding correlated well with the study performed by Conceicao et al., (1998) [6].

Conclusion

Caudal block with 0.2% Ropivacaine resulted in equal duration of analgesia with less duration of motor block as compared with 0.25% caudal Bupivacaine, without an increase in incidence of side effects when administered pre-operatively in a volume of 0.5 ml/kg to children undergoing lower abdominal and urogenital surgeries.

References

1. Scott DB, Lee A, Fagan D, Bowler GM, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. AnesthAnalg. 1989; 69:563–69.
2. Arthur GR, Feldman HS, Covino BG. Comparative pharmacokinetics of bupivacaine and ropivacaine, a new amide local anesthetic. AnesthAnalg. 1988; 67:1053–58.
3. McGlade DP, Kalpokas MV, Mooney PH, Chamley D, Mark AH. A comparison of 0.5% Ropivacaine and 0.5% Bupivacaine for axillary brachial plexus anaesthesia. Anaesth Intensive care. 1998;26:515–20.
4. Thornton KL, Sacks MD, Hall R, Bingham R. Comparison of 0.2% Ropivacaine and 0.25% Bupivacaine for axillary brachial plexus blocks in paediatric hand surgery. PaediatrAnaesth. 2003; 13:409–12.
5. Kay B. Caudal block for post-operative pain relief in children. Anaesthesia 1974;29:610-614.
6. M.J. D.A. Conceicao, L. Coelho. Caudal anaesthesia with 0.375% Ropivacaine in comparison with 0.375% Bupivacaine in paediatric patients – British Journal of anaesthesia. 1998;80:507-508.
7. Hickey R, Hoffman J, Ramamurthy S. A comparison of ropivacaine 0.5% and bupivacaine 0.5% for brachial plexus block. Anesthesiology. 1991;74: 639-42.
8. Casati A, Fanelli G, Albertin A, Deni F, Anelati D, Antonino FA, Beccaria P. Interscalene brachial plexus anesthesia with either 0.5% ropivacaine or 0.5% bupivacaine. Minerva Anestesiol. 2000 Jan-Feb;66(1-2):39-44.
9. Raikwar Surendra, Sonal Awasya, Gupta Pankaj. Comparative clinical evaluation of 0.5% ropivacaine and 0.5% bupivacaine for brachial plexus block via supraclavicular approach for upper limb surgeries. Journal of Evolution of Medical and Dental Sciences 2013;2(47):9167- 73.

Revised Rates for 2019 (Institutional)

Title of the Journal	Frequency	India(INR) Print Only	India(INR) Online Only	Outside India(USD) Print Only	Outside India(USD) Online Only
Dermatology International	Semiannual	5500	5000	430	391
Gastroenterology International	Semiannual	6000	5500	469	430
Indian Journal of Anatomy	Quarterly	8500	8000	664	625
Indian Journal of Anesthesia and Analgesia	Bi-monthly	7500	7000	586	547
Indian Journal of Cancer Education and Research	Semiannual	9000	8500	703	664
Indian Journal of Communicable Diseases	Semiannual	8500	8000	664	625
Indian Journal of Dental Education	Quarterly	5500	5000	430	391
Indian Journal of Diabetes and Endocrinology	Semiannual	8000	7500	597	560
Indian Journal of Genetics and Molecular Research	Semiannual	7000	6500	547	508
Indian Journal of Hospital Administration	Semiannual	7000	6500	547	508
Indian Journal of Hospital Infection	Semiannual	12500	12000	938	901
Indian Journal of Medical & Health Sciences	Semiannual	7000	6500	547	508
Indian Journal of Pathology: Research and Practice	Bi-monthly	12000	11500	938	898
Indian Journal of Preventive Medicine	Semiannual	7000	6500	547	508
International Journal of Neurology and Neurosurgery	Quarterly	10500	10000	820	781
International Physiology	Triannual	7500	7000	586	547
Journal of Cardiovascular Medicine and Surgery	Quarterly	10000	9500	781	742
Journal of Global Medical Education and Research	Semiannual	5900	5500	440	410
Journal of Global Public Health	Semiannual	12000	11500	896	858
Journal of Microbiology and Related Research	Semiannual	8500	8000	664	625
Journal of Organ Transplantation	Semiannual	26400	25900	2063	2023
Journal of Orthopedic Education	Triannual	5500	5000	430	391
Journal of Pharmaceutical and Medicinal Chemistry	Semiannual	16500	16000	1289	1250
Journal of Practical Biochemistry and Biophysics	Semiannual	7000	6500	547	508
Journal of Radiology	Semiannual	8000	7500	625	586
New Indian Journal of Surgery	Bi-monthly	8000	7500	625	586
Ophthalmology and Allied Sciences	Triannual	6000	5500	469	430
Otolaryngology International	Semiannual	5500	5000	430	391
Pediatric Education and Research	Quarterly	7500	7000	586	547
Physiotherapy and Occupational Therapy Journal	Quarterly	9000	8500	703	664
Urology, Nephrology and Andrology International	Semiannual	7500	7000	586	547
Indian Journal of Maternal-Fetal & Neonatal Medicine	Semiannual	9500	9000	742	703
Indian Journal of Obstetrics and Gynecology	Quarterly	9500	9000	742	703
Indian Journal of Emergency Medicine	Quarterly	12500	12000	977	938
Indian Journal of Trauma and Emergency Pediatrics	Quarterly	9500	9000	742	703
Journal of Emergency and Trauma Nursing	Semiannual	5500	5000	430	391
Indian Journal of Forensic Medicine and Pathology	Quarterly	16000	15500	1250	1211
Indian Journal of Forensic Odontology	Semiannual	5500	5000	430	391
Indian Journal of Legal Medicine	Semiannual	8500	8000	664	625
International Journal of Forensic Sciences	Semiannual	10000	9500	781	742
Journal of Forensic Chemistry and Toxicology	Semiannual	9500	9000	742	703
Community and Public Health Nursing	Triannual	5500	5000	430	391
Indian Journal of Surgical Nursing	Triannual	5500	5000	430	391
International Journal of Pediatric Nursing	Triannual	5500	5000	430	391
International Journal of Practical Nursing	Triannual	5500	5000	430	391
Journal of Gerontology and Geriatric Nursing	Semiannual	5500	5000	430	391
Journal of Nurse Midwifery and Maternal Health	Triannual	5500	5000	430	391
Journal of Psychiatric Nursing	Triannual	5500	5000	430	391
Indian Journal of Ancient Medicine and Yoga	Quarterly	8000	7500	625	586
Indian Journal of Law and Human Behavior	Semiannual	6000	5500	469	430
Indian Journal of Medical Psychiatry	Semiannual	8000	7500	625	586
Indian Journal of Biology	Semiannual	5500	5000	430	391
Indian Journal of Library and Information Science	Triannual	9500	9000	742	703
Indian Journal of Research in Anthropology	Semiannual	12500	12000	977	938
Indian Journal of Waste Management	Semiannual	9500	8500	742	664
International Journal of Political Science	Semiannual	6000	5500	450	413
Journal of Social Welfare and Management	Triannual	7500	7000	586	547
International Journal of Food, Nutrition & Dietetics	Triannual	5500	5000	430	391
Journal of Animal Feed Science and Technology	Semiannual	7800	7300	609	570
Journal of Food Additives and Contaminants	Semiannual	5000	4500	391	352
Journal of Food Technology and Engineering	Semiannual	5000	4500	391	352
Indian Journal of Agriculture Business	Semiannual	5500	5000	413	375
Indian Journal of Plant and Soil	Semiannual	6500	6000	508	469

Terms of Supply:

1. Agency discount 12.5%. Issues will be sent directly to the end user, otherwise foreign rates will be charged.
2. All back volumes of all journals are available at current rates.
3. All Journals are available free online with print order within the subscription period.
4. All legal disputes subject to Delhi jurisdiction.
5. Cancellations are not accepted orders once processed.
6. Demand draft / cheque should be issued in favour of "**Red Flower Publication Pvt. Ltd.**" payable at **Delhi**
7. Full pre-payment is required. It can be done through online (http://rfppl.co.in/subscribe.php?mid=7).
8. No claims will be entertained if not reported within 6 months of the publishing date.
9. Orders and payments are to be sent to our office address as given above.
10. Postage & Handling is included in the subscription rates.
11. Subscription period is accepted on calendar year basis (i.e. Jan to Dec). However orders may be placed any time throughout the year.

Order from

Red Flower Publication Pvt. Ltd., 48/41-42, DSIDC, Pocket-II, Mayur Vihar Phase-I, Delhi - 110 091 (India),
Mobile: 8130750089, Phone: 91-11-45796900, 22754205, 22756995 E-mail: sales@rfppl.co.in, Website: www.rfppl.co.in

Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(1) (Part - II): 207-210
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.29

Intrathecal Midazolam for Post Operative Pain Relief in Lower Segment Caesarean Section

Suman Gupta[1], Preeti Goyal[2]

[1]Associate Professor [2]Professor, Department of Anaesthesiology, Gajra Raja Medical College, Madhya Pradesh 474009,India.

Abstract

Background: Postoperative pain relief is one of the important component which needs to be managed in patients undergoing lower segment cesarean section. Midazolam is a drug which can be used for postoperative pain relief as an adjunct to anaesthetic medication. *Methods:* The study was conducted at tertiary care health institute. Total of 90 patients, 30 patients in each group were included in the study. Each group was evaluated for onset, intensity and duration of sensory and motor block, central side effects, time to first pain medication. Visual analog scale was used to assess the postoperative pain. *Result:* Time to first pain medication was significantly prolonged in group XM_1 (n=30 with 2 mg midazolam) as compared to group X (n=30, 5% xylocaine hydrochloride). Nevertheless VAS at first pain medication was comparable in all the three groups. The side effects were no different in three groups. *Conclusion:* Addition of intrathecal midazolam at these dosages appears safe and has clinically proven analgesic properties with no major side effects.

Keywords: Intrathecal Midazolam; Post-Operative; Pain Relief; Xylocaine.

How to cite this article:

Suman Gupta, Preeti Goyal. Intrathecal Midazolam for Post Operative Pain Relief in Lower Segment Caesarean Section. Indian J Anesth Analg. 2019;6(1):207-10.

Introduction

Pain is an unpleasant sensory and emotional experience associated with actual and potential tissue damage or described in term of such damage. The distress and pain which a patient often experiences in immediate post-operative period is beyond description. Post-operative pain relief can improve functionality, reduce physiological and emotional morbidity and improve quality of life of the patients. As an anaesthetist it is our duty as well as priviledge to use all legitimate means to bring down the physical sufferings of patient in terms of pain not only during operation itself but also during post-operative period. Various modalities available for pain relief include intra muscular injection of strong analgesics, nerve block using local anaesthetic, intrathecal injection of certain drugs like opiods, ketamine, benzodiazepine either via subarachnoid or epidural route. They have advantages, as they reduce the dose of local anaesthetic medications; provide long lasting post-operative analgesia with reduced incidence of central nervous system depression, motor effects or hypotension [1]. Midazolam, synthesized by Walsar and colleagues in 1976, was the first clinically used

Corresponding Author: Suman Gupta, Associate Professor, Department of Anaesthesiology, Gajra Raja Medical College, Madhya Pradesh 474009,India.
E-mail: sumangupta02@rediffmail.com
Received on 13.11.2018, **Accepted on** 03.12.2018

water-soluble benzodiazepine [2]. It is also the first benzodiazepine that was produced primarily for use in anaesthesia.

Midazolam has marked analgesic properties with minimal adverse effect. It can be used either epidurally or intrathecally [3]. Hence, it was planned to do a comparative evaluation of inrathecal preservative free midazolam and 5% lignocaine in patients undergoing lower segment caesarean section for its analgesic properties.

Material and Methods

The study was conducted at tertiary care health institute of northern India. Patients between age groups of 20-35 years who underwent lower section cesarean section were divided into three groups of 30 each to receive either 1.2 ml of 5% heavy Xylocaine Hcl for group X, one mg of midazolam in 0.2 ml along with 1.2 ml of 5% heavy Xylocaine Hcl for group XM_1 and 2 mg of midazolam in 0.4 ml along with 1.2 ml of 5% heavy XylocaineHcl for group XM_2. All patients received an uniform premedication of injection Glycopyrrolate bromide 0.2 mg I.M. Injection Ondeansetron 4 mg I/V, injection Metoclopromide 10 mg I/V were given 30 minutes prior to operative procedure upon arrival into the operation theater. Ringer Lactate solution 500 ml was infused as a preload, followed by dextrose 5%. Under all aseptic conditions lumber puncture was performed at l2-L3 space and following drugs were injected.

Group X: 1.2 ml of 5% heavy Xylocaine Hcl

Group XM_1: 1 mg of midazolam in 0.2 ml along with 1.2 ml of 5% heavy Xylocaine Hcl

Group XM_2: 2 mg of midazolam in 0.4 ml along with 1.2 ml of 5% heavy Xylocaine Hcl.

The onset, intensity and duration of analgesia and motor loss, sedationscore, time of first pain medication, duration of surgery were recorded. Changes in pulse rate, systolic blood pressure, diastolic blood pressure, respiratory rate were recorded every minute till 5 minutes, then every 5 minutes till 15 minutes, then every 10 minutes until completion of surgery.

Measurement of analgesia

Analgesia was assessed by pinprick method. Onset time was taken as time from injection of drug into subarachnoid space and complete sensory loss. From this point to the time when sensation recorded to segments as noted as duration of Analgesia.

Measurement of motor loss

Motor loss was assessed by straight leg raising test. Time interval between injection of drug into subarachnoid space to patient's inability to lift the leg was taken as onset time. From this point to the time when patient was able to lift leg was recorded as duration of motor loss.

Time to first medication

This was the time taken from the onset of analgesia to the time at first pain medication. Assessment of Pain was done by patients themselves and for this assessment visual analogue scale (VAS) was used (Pilowsky and Bond 1956). During the pre-operative interview subjects were familiarized with the recording of scale. VAS rating was done as follows; 0 as No pain, 1-25 as mild pain, 26-50 as moderate pain, 51-75 as severe pain and 76-100 as very severe pain.

All the recorded variables were recorded in predesigned proforma. The variables were checked for normal distribution. The continuous variables were presented as mean±SD. The continuous variable related to time of sensory and motor blockade and the post operative pain relief were analysed using Annova test. p value <0.05 was considered as statistically significant.

Results

There were total of 90 patients involved in the present study with 30 patients in each group. All the three groups were demographically comparable with respect to age, sex and type of surgery performed. In all three groups there was statically insignificant alteration in pulse rate, systolic and diastolic blood pressure and respiratory rate.

Sensory and motor block

All the ninety patients had intense grade three analgesia after the intrathecal administration of drugs in Group X, 10 patients each (33%) had analgesia upto T7-T8 and T10. In group XM_1, 17 patients (56.66%) had highest level upto T7, where as in Group XM_2 19 patients (63.33%) had level upto T6.

There was no significant difference in onset time intensity and duration of sensory and motor block, central side effect in intergroup statistical comparison (Table 1). The time of first pain medication was significantly delayed in group XM_1 & XM_2 as compared to X ($p<0.001$) (Table 2)

Table 1: Time of onset of sensory block and time of onset, degree, duration of motor block

Grade	Group X	Group XM_1	Group XM_2
Sensory block			
onset time (min)	2.05 +0.58	2.016 + 0.46	2.0 +0.70
Motor block			
onset time (min)	4.8+0.89	4.266+0.79*	4.233+0.40*
Degree of motor blockade	2.03 + 0.40	2.13+0.33	2.23+0.42
Duration of motor blockade (min)	92.16 + 6.53	94.06 + 10.46	92.36+9.4

*p value <0.05 (statistical significant); Group X = 5% Xylocaine hydrochloride; Group XM_1 = 5% Xylocaine hydrochloride ±1 mg midazolam; Group XM_2 = 5% Xylocaine hydrochloride ±2 mg midazolam

Table 2: Intergroup comparison of post operative pain relief

Parameters	Grade X	Grade XM_1	Grade XM_2
Time of first pain medication in hours	2.9+0.63	3.99+0.62**	4.37+5.09**
VAS at first pain medication	35+4.3	36+5.76	34+5.2

**p value <0.001 (statistically highly significant)

There was no incidence of bradycardia, sedation, dizziness, pruritis, respiratory depression neurological deficit. Thus addition of intrathecal midazolam is devoid of any side effects.

Discussion

The present study entitled "Evaluation of intrathecal midazolam (preservative free) for postoperative pain relief in lower segment caseraean" section was carried out to assess the effects of Intrathecal midazolam and to study the sideeffects and complication related to the use of this drug in different dosage during spinal anaethesia.

The onset of analgesia (mean±SD) recorded in the present study was 2.05±0.58 minutes, 2.016±0.46 and 2.0±0.7 minute in group X, XM_1, and XM_2 respectively and in the intergroup comparison the differences were found to be statistically insignificant (p>0.05). No local anaesthetic effect of midazaolm on afferent nerve going into spinal cord has been reported [4,5]. The onset and duration of motor block (mean±SD) in group X was 4.8±0.79 and 94.06±10.46 minutes and in group XM_2 was 4.23±0.40 and 92.36±9.4 minutes. The differences were found to be statistically significant (p<0.05).

Thus it is reasonable to assume that the midazolam acting at the spinal cord level caused synergistic effect in muscle relaxation produced by local anaesthetic action [6-8].

In this study the time to first pain medication in hours (mean±SD) was 2.9±0.63 minutes, 3.99±0.62 minutes and 4.37±5.09 minutes in group X, group XM_1 and group XM_2 respectively. The differences were statistically highly significant (p<0.001). Our results were similar to various authors who have found midazolam as an effective analgesic by intrathecal route [3,4,9]. The mean±SD of VAS at first pain medication in three groups are 35±4.3, 36±5.76 and 34±5.2 in the control group X, Group XM_1 and Group XM_2 respectively. The intergroup comparison is insignificant (p>0.05).

Interaction of intrathecal midazolam with non opiod GABA receptor complex in dorsal horn have been attributed to anti-nociceptive effect [10-12]. There were no significant changes in hemodynamic parameters in any of the 3 groups. Hypotension is a normalsequelae of centro-neuraxial blockade and it is quite clear that addition of midazolam has not increased the severity of hypotension. Majority of workers who evaluated the hemodynamic effects of epidural/intrathecal midazolam have found it safe [4,13].

Conclusion

From this study it can be concluded that both of intrathecal midazolam 1 mg and 2 mg are effective in increasing the analgesic effects of spinal blockade with xylocaine. Both the doses were able to significantly prolong the time to first pain medication and it was found to be better with increasing dose. Addition of midazolam with xylocaine intrathecally did not have any deleterious effects on the hemodynamic stability. No side effects attributed to midazolam were identified. Thus intrathecal midazolam at these dosages appears safe and has clinically detectable analgesic properties.

References

1. Reves JG. Midazolam: Pharmacology and uses. Anaesthesiology. 1985;62:310-324.
2. Greenblatt DJ. Drug therapy: Current status of benzodiazepines. The New Eng J Med. 1983;309:354-8.
3. Kim MH, Lee YM. Intrathecal midazolam increases the analgesic effects of spinal blockade with bupivacaine in patients undergoing haemorrhoidectomy. Br JrAnaesth. 2001;86:77-9.
4. Batra YK, Jain K, Char P, Dhillon MS, Shabeen B,

Reddy GM. Addition of Intrthecal midazolam to bupivacaine produces better post operative analgesia without prolonging recovery. Int Journal ClinPharmacolTher. 1999;37:519-23.

5. Good Child CS, Nobel J. The effects of Intrathecal midazolam on sympathetic nervous system reflexes in Man: A pilot study. British Journal Clin Pharmacol 1987;23:279-85.
6. Behar M, Cohen ML, Grinshpoon Y, Kopolovic U, Hervert M, Nass D, Chanimov M. An investigation of the possible neurotoxic effects of intrathecal midazolam combined with fentanyl in the rat. Eurp Jr Anaesthesiology. 1998;14:690-701.
7. Dahn LS, Beric A, Dimitrijevic MR, Wall PD. Direct spinal effect of a Benzodiazepine (Midazolam) on spasticity in Man. Stereotoit Funet Neurosurg. 1989;52:85-94.
8. SiCafried J, Rea GI. Intrathecal application of drugs for muscle hypertonia. Scand J Rehabil Med 1998;17:145-8.
9. Nishiyama T Matsukawa T, Hanaoaka K, Continuous epidural administration of Midazolam and bupivacaine for post operative analgesia. Acta Anasethesiol Scand. 1999;43;568-72.
10. Edward M, Serrao JM, Gent JP, Goodchild CS. On the mechanism by which midazolam causes spinally mediated analgesia. Anesthesiology. 1990;73:273-7.
11. Niv D, Whitwam JG, Loh L. Depressionof nociceptive reflexes by intrathecal administration of midazolam. Br JrAnaesth. 1995;55:541-47.
12. Serrao JM, Gent JP, Goodchild CS. Naloxone reverses the spinal analgesic effects of midazolam. Br J Anaesth. 1989;62:233–4.
13. Goodchhild CS, Serrao JM. Intrathecal midazolam in the rats. Evidence for spinally mediated analgesia. Br J Anaesth. 1987;59:1563-70.

Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(1) (Part - II): 211-217
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.30

Comparative Study of Nitroglycerin and Dexmedetomidine in Patients Undergoing Endoscopic Resection of Nasopharyngeal Fibroangioma

Syed Akram Moin[1], Thirukkovalluri Ravi[2]

[1]Assistant Professor [2]Associate Professor, Department of Anesthesiology, Osmania Medical College/ENT Hospital, Koti, Hyderabad, Telangana 500095. India.

Abstract

Introduction: Nasopharyngeal Fibroangioma (NPF) is a rare, benign, but locally invasive tumor removed with nasal endoscopy which is minimally invasive and provides a magnified view of the tumor. Hypotensive anaesthesia technique is required to assist in decreasing blood loss and providing bloodless clear field to facilitate surgery. *Aim:* To compare Nitroglycerin and Dexmedetomidine groups for hypotensive anaesthesia in patients undergoing endoscopic resection of Nasopharyngeal Fibroangioma. *Materials and Methods:* This is a prospective, randomized, single blinded study conducted on 40 patients between the age group of 10-20 years undergoing endoscopic resection of Nasopharyngeal Fibroangioma. The patients were randomly divided into two groups of 20 patients each. Group D – Patients who received 'Dexmedetomidine' Group N – Patients who received 'Nitroglycerin'. *Results:* There was no statistically significant difference between the two groups regarding mean arterial pressures. There was statistically significant difference between the two drug groups regarding pulse rate. The mean pulse rate in Dexmedetomidine group was significantly less than in Nitroglycerin group. The average blood loss was more with Nitroglycerin when compared to Dexmedetomidine. *Conclusion:* Nitroglycerine and Dexmedetomidine can be used safely for maintaining hypotensive anaesthesia to achieve the target mean arterial pressure around 60-70 mm/Hg. The blood loss was significantly less in Dexmedetomidine group. Dexmedetomidine was superior to Nitroglycerin in reducing blood loss during the resection.

Keywords: Dexmedetomidine; Nitroglycerin; Nasopharyngeal Fibroangioma.

How to cite this article:

Syed Akram Moin, Thirukkovalluri Ravi. Comparative Study of Nitroglycerin and Dexmedetomidine in Patients Undergoing Endoscopic Resection of Nasopharyngeal Fibroangioma. Indian J Anesth Analg. 2019;6(1):211-217.

Introduction

Nasopharyngeal Fibroangioma (NPF) is a rare, benign, but locally invasive tumor, with an incidence of 1:150000, almost exclusively encountered in the adolescent males [1]. Surgery is considered to be the gold standard treatment. These are enormously vascular tumors and open surgical resection is associated with significant blood loss and postoperative morbidity. Recently, endoscopic excision has been widely employed for the excision of small and medium sized angiofibromas. Nasal endoscopy is minimally invasive and provides a magnified view of the tumor. It is also associated with less postoperative morbidity and low recurrence rate [2]. The major problem with endoscopic surgery is that even minimal bleeding can interfere with endoscopic

Corresponding Author: Thirukkovalluri Ravi, Associate Professor, Department of Anesthesiology, Osmania Medical College/ENT Hospital, Koti, Hyderabad, Telangana 500095, India.

E-mail: drtravi@yahoo.com

Received on 08.11.2018, **Accepted on** 03.12.2018

vision. Thus, hypotensive anaesthesia is required to assist in decreasing blood loss and providing a bloodless clear field to facilitate surgery. Controlled (deliberate/induced) hypotension is a technique wherein the arterial blood pressure is lowered in a deliberate but controllable mannerto minimize surgical blood loss and enhance the operative fieldvisibility [3]. There are several pharmacological and non-pharmacological techniques for inducing hypotension. The various pharmacological interventions include volatile anaesthetics, direct-acting vasodilator drugs, ganglion blocking drugs, alpha blockers, beta blockers, combined alpha and beta blockers, calcium channel blockers, propofol, magnesium sulphate, alpha-2 agonists, prostaglandins, tranexamic acid etc. [4]. Nitroglycerin is a direct acting peripheral vasodilator, which primarily dilates capacitance vessels, reducing venous return with concomitant reduction in stroke volume and cardiac output. Dexmedetomidine is an α2 adrenergic receptor agonist causes controlled hypotension by its centraland peripheral sympatholytic action, results in decrease in blood pressure [5]. Hence the present study is undertaken to compare Nitroglycerinvs. Dexmedetomidine infusion for hypotensive anaesthesia in endoscopic resection of Nasopharyngeal Fibroangioma.

Materials and Methods

This is a prospective, randomized, single blinded study conducted on 40 patients between the age group of 10-20 years undergoing endoscopic resection of Nasopharyngeal Fibroangioma in Government ENT Hospital, Osmania Medical College, Hyderabad. After approval by the institutional ethical committee, written informed consent was obtained from the patients during the pre-anaesthetic evaluation. Result values were recorded using a presetproforma.

Inclusion Criteria: ASA Grade I or II, Aged between 10–20 years

Exclusion Criteria: ASA Grade III and IV, Coagulopathy or on Anti-coagulation, with known End – Organ damage, History of known drug allergy to any of the drugs used in this study.

Investigations done: CBC, BT, CT, Blood grouping and typing, Random Blood sugar, Serum Urea and Serum Creatinine, Chest X-Ray, ECG, HIV, HBsAg. Patients included in this study were randomly assigned to receive either Dexmedetomidine (Group D, n=20) or Nitroglycerin (Group N, n=20). In the operating room, following monitors were used as Pulse Oximetry, Blood Pressure cuff for non-invasive blood pressure monitoring, 5 lead ECG, $EtCO_2$ (after intubation). Two cannulas were inserted, one for infusion of Dexmedetomidine or Nitroglycerin infusion and the other for administration of fluids and other drugs. A urinary catheter was inserted.

All the patients were premedicated with Inj. Glycopyrrolate 0.04 mg/Kg, Inj. Ondansetron 0.08 mg/ Kg. In Group- D an infusion of Dexmedetomidine was made by adding 200 µg (2 ml) of Dexmedetomidine to 100 ml of normal saline, administered in paediatric volumetric IV burette set, making it to a final concentration of 2 µg/ml. The infusion was then started; with a loading dose of 1 µg/kg over 15 min followed by a maintenance infusion at 0.5 µg/kg/hr titrated according to the patients desired target blood pressure (21). In Group- N, patients received fentanyl (2 ug/Kg) before induction followed by an infusion of NTG, made by adding 25 mg (5 ml) of NTG to 100 ml of normal saline, administered in paediatric volumetric IV burette set, making it to final concentration of 250 µg/ml. The infusion was then started at the rate of 0.5 µg/kg/min and titrated in between 0.5-5 µg/kg/min according to the target blood pressure.

Both the study groups received standard anaesthetic technique with Inj. Thiopentone sodium 3-5 mg/ kg titrated to loss of eyelash reflex. Endotracheal intubation was facilitated with Inj. Suxamethonium (1.5 mg/kg) and intubation was done with suitable sized cuffed tube. All the patients were mechanically ventilated with 33:66 O_2/N_2O mixtures and Desflurane 4-6% to maintain $EtCO_2$ within normal range of 30-35 mm/ Hg. Muscle relaxation was continued by Inj. Vecuronium. Respiratory rate (RR) and Tidal Volume (TV) were adjusted according to body weight to maintain normocapnia. Patients received normal saline and dextrose; were placed in a 15^0 Reverse trendelenburg position to improve venous drainage and oro-pharyngeal pack was placed. The MAP was then gradually reduced in both the groups to achieve and maintain the target MAP of 60-70 mm/Hg. Patients who developed severe hypotension (MAP < 55 mmHg) were observed by discontinuation of the hypotensive agents and reducing the concentration of Desflurane. If the MAP did not improve 6mg bolus of mephentermine was given intravenously. If any patients developed bradycardia (<50 bpm) then they received Inj. Atropine 0.6 mg I.V.

Infusion of the hypotensive agent was stopped

10 minutes before the end of surgery. Any residual neuromuscular block was antagonized with Inj. Neostigmine 50 µg/kg & Glycopyrrolate 10 µg/kg. Continuous monitoring was carried out throughout the procedure for heart rate, cardiac rhythm, urine output, MAP, oxygen saturation& $EtCO_2$. The urine output was maintained between 0.5 ml/kg/hr and 1 ml/kg/hr in patients.

Observations

The hemodynamic variables were recorded as pulse rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, preoperatively (baseline parameters & intra-operatively at an interval of every 10 mins until the completion of surgery). After the extubation and full recovery, patients were transferred to the post anaesthesia care unit (PACU). The surgery lasted for 150 mins in almost all the patients, so pulse rate and blood pressures and mean arterial pressures were recorded for this duration.

The Statistical analysis was done using Mean, Standard deviation and Independent t- test (for hemodynamic parameters). All recorded data were entered using MS Excel software and analysed using SPSS 16 version software for determining the statistical significance. p values < 0.05 were considered to be statistically significant.

Results

Table 1: Distribution Patient Characteristics in Study Groups

Groups	N	Mean	Standard Deviation	p Value
Age Distribution				
Group- D	20	15.94	±2.26	0.4373
Group- N	20	15.33	±2.64	
Weight Distribution				
Group D	20	45.29	±9.75	0.8192
Group N	20	45.96	±8.63	

The range of ages was between 10–20 years in both the study groups.

The range of weight was 28–60 Kg in both the study groups.

There was no statistically significant difference (p>0.05) between the two groups in age and weight distributions (Table 1).

There is statistically significant difference between the two groups (p <0.05), when the pulse rates were compared (Fig. 1).

Intraoperatively, there is no statistically significant difference between the two groups (p>0.05), when systolic blood pressures were compared (Fig. 2).

Intraoperatively, there was no statistically significant difference between the two groups (p >0.05), when the diastolic blood pressures were compared (Fig. 3).

Intraoperatively, there was no statistically significant difference between the two groups (p>0.05), when the Mean Arterial Pressures were compared (Fig. 4).

The blood loss was measured as blood volume in suction bottle and amount soaked in swabs. The mean blood loss in Group D was less than the

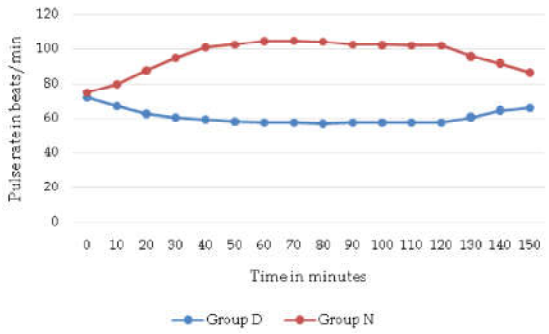


Fig. 1: Hemodynamic Variables Mean Pulse Rates Between Study Groups

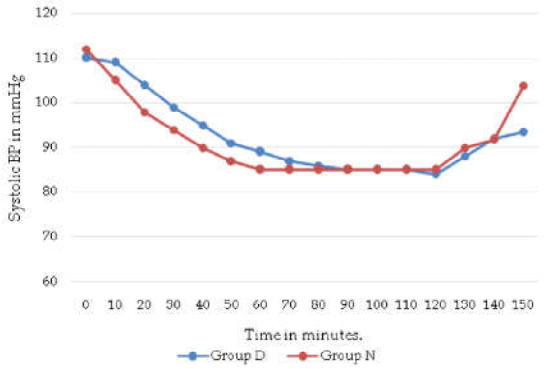


Fig. 2: Mean Systolic Blood Pressure Between Study Groups

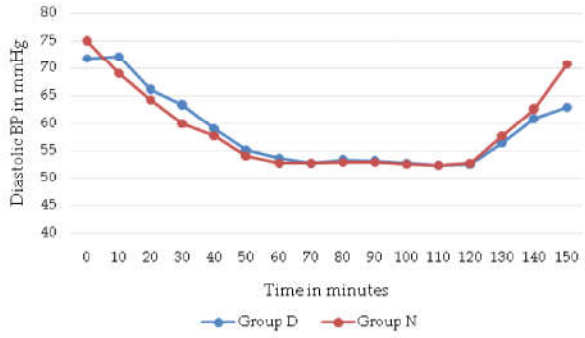


Fig. 3: Mean Diastolic Blood Pressure Between Study Groups

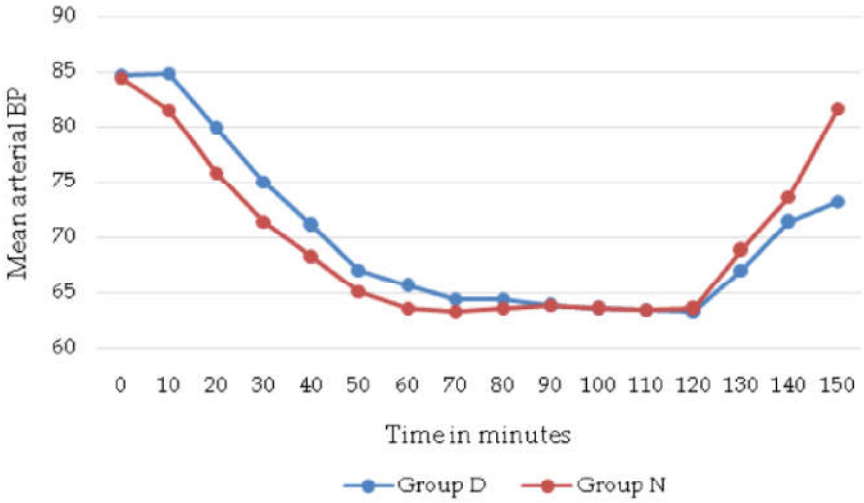


Fig. 4: Mean Arterial Pressure Between Study Groups

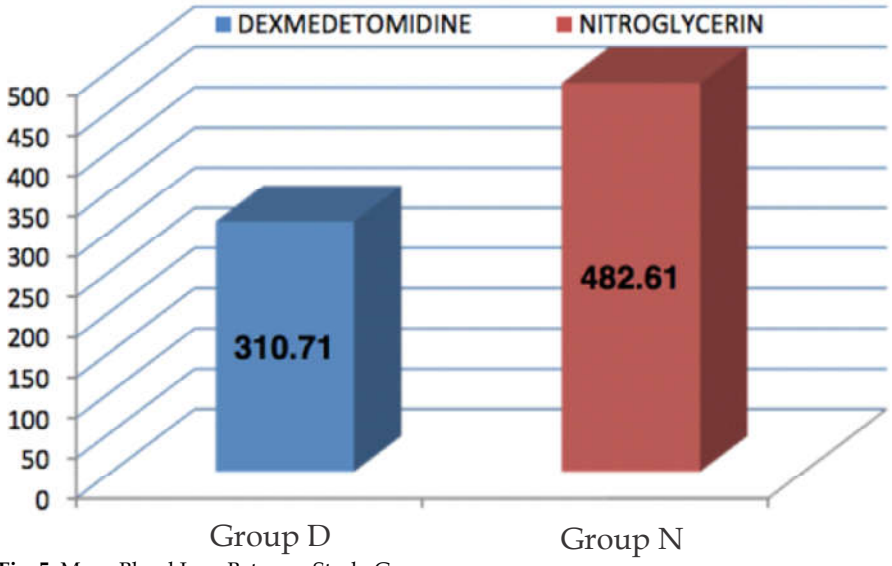


Fig. 5: Mean Blood Loss Between Study Groups

average blood loss in Group N. The difference in blood loss between both the groups was considered to be statistically significant (Fig. 5).

Discussion

Nasopharyngeal Fibroangioma is the most common benign neoplasm of the nasopharynx. It is almost exclusively encountered in adolescent males. They are enormously vascular tumors and open surgical resection is associated with significant blood loss and postoperative morbidity. Recently, endoscopic excision has been widely employed for the excision of angiofibromas. The major problem with endoscopic surgery is that even minimal bleeding can interfere with endoscopic vision. Thus hypotensive anaesthesia is required to assist in decreasing blood loss and providing a bloodless, clear field to facilitate surgery.

Induced or controlled hypotension is a method by which the arterial blood pressure is decreased in a predictable and deliberate manner. The intent of deliberate hypotension is to reduce bleeding and thus facilitate surgery and to decrease the amount of blood transfused.

Care was taken to protect the pressure points by padding. A hypotensive technique reduces the peripheral circulation. This is especially important in areas overlying weight-bearing and bony prominences. Hence, additional supportive pads were placed beneath the patient with special attention paid to the occiput, scapulae, sacrum, elbows and heels. Monitoring of ECG, especially

the V5 lead with ST segment analysis was done to detect cardiac ischemia. Prevention of hypercarbia and hypocapnia are essential in hypotensive anaesthesia. Hypothermia was avoided because it decreases the effectiveness of vasodilators and increases the dose requirements if compensatory vasoconstriction occurs. Proper fluid therapy is essential during hypotensive anaesthesia. The aim of induced hypotension is to lower MAP while maintaining adequate perfusion to all vital organs. Thus, preoperative fluid status was assessed and corrected.

Hypotension was only carried out to that level needed to reduce bleeding and only for that time of the surgery where it is of benefit in reducing significant blood loss. Head end was slightly elevated. Position of the patient is critical to ensure success of the controlled hypotensive technique. Elevation of the site of operation allows easy venous drainage from the site of surgery. This is critical to ensure a bloodless field. But exaggerated head end elevation compromises blood supply to brain during hypotensive anaesthesia, so head end elevation was only limited to 15 degrees.

In this prospective randomized study comparing Dexmedetomidine and Nitroglycerin groups, efforts were made to provide this optimal surgical field. Both the drugs were equally effective in achieving MAP (Mean Arterial Pressure) of 60-70 mm/Hg. The average blood loss was more with Nitroglycerin when compared to Dexmedetomidine. This can be due to increased heart rate & prolongation of bleeding time by NTG due to inhibition of platelet aggregation because similardecrease in mean arterial pressure is achieved by both the drugs. Dexmedetomidine ensured good surgical conditions during endoscopic resection of NPF.

Dexmedetomidine loading dose (1 µg/kg) was given in 15 min before induction of anaesthesia and infusion started after the loading dose. There was significant decrease in MAP and HR. This Dexmedetomidine induced hemodynamic profile can be attributed to the known sympatholytic effect of α2 agonists. The α2-receptors are involved in regulating the autonomic and cardiovascular systems. Alpha 2 receptors are located on blood vessels, where they mediate vasoconstriction on stimulation, and in the brain on sympathetic terminals, where they inhibit, norepinephrine release. At lower doses, the dominant action of α2 agonists is sympatholysis by their central action inhibiting norepinephrine release [23]. Higher doses may cause transient increase in blood pressure due to predominant action on peripheral α2-receptors causing vasoconstriction The efficacy of Dexmedetomidine in providing better surgical field and less blood loss during controlled hypotension was previously reported during tympanoplasty, septoplasty and maxillofacial surgeries as well [24].

Basar et al., [6] investigated the effect of single dose of Dexmedetomidine 0.5 µg/kg administration 10 min before induction of anaesthesia and reported significant reduction in MAP and HR. No other analgesic was used in the Group-D (Dexmedetomidine group); because Dexmedetomidine has inherently got analgesic property due to its action in the locus ceruleus of the brain stem [7,8]. It has been shown to stimulate α2 receptors directly in the spinal cord, thus inhibiting the firing of nociceptive neurons. Even peripheral α2 adrenoceptors may mediate antinociception. No other agent for anxiolysis was also used because Dexmedetomidine has anxiolytic property as well. The efficacy of Dexmedetomidine, in terms of providing an ideal surgical field during control hypotension, was previously reported during middle ear surgery and maxillofacial surgery with predictable hemodynamic effects. The results of the present study showed the same results. The optimal anaesthetic technique to reduce blood loss at the surgical field seems to cause relative bradycardia and associated hypotension.

Ulger et al., [9] compared Dexmedetomidine with Nitroglycerine to achieve controlled hypotension in patients scheduled for middle ear surgery. The infusion rate of drugs was titrated to maintain a mean arterial pressure between 65 and 75 mmHg. They concluded that Dexmedetomidine was better for maintaining hemodynamic stability and a drier surgical field, and was devoid of reflex tachycardia and rebound hypertension. The results of the present study are in accordance with these data.

In the current study, the induction dose of Thiopentone sodium was significantly lower in the Group- D (Dexmedetomidine group) in most of the patients. This effect coinciding with the result of Peden et al., [10] who reported that Dexmedetomidine caused a reduction in the overall dose of induction agent required to produce loss of consciousness. This is because of the sedative and hypnotic properties of Dexmedetomidine.

Guven et al., and Goksu et al., [11,12] reported better hemodynamic stability and visual analog scale pain scores; as well as a clear surgical field and few side effects, with dexmedetomidine infusion in functional endoscopic sinus surgery. In Group-2, Fentanyl 2 ug/Kg was given 3 minutes before induction. Nitroglycerin infusion (0.5-5

ug/Kg/min) was started after induction-intubation.

In the present study, infusion rate was based on the patient's body weight and hemodynamic response and blood pressure was maintained within the range of 60-70 mmHg. Nitroglycerin acts predominantly on venous capacitance vessels, primarily decreases preload to the heart, in addition, it also decreases systemic vascular resistance and afterload. The production of controlled hypotension using this drug depends more on intravascular fluid volume. Excessive decreases in diastolic blood pressure may decrease coronary blood flow. These decreases in diastolic blood pressures may also evoke baroreceptor-mediated reflex increases in sympathetic nervous system activity manifesting as tachycardia and increased myocardial contractility. Nitroglycerin produces a dose-related prolongation of bleeding time that parallels the decrease in blood pressure. It inhibits platelet aggregation. Increased bleeding time could also be the result of vasodilation secondary to a direct effect of Nitroglycerin on vascular tone.

Karl-Erik Karlberg and associates [13] assessed the influence of intravenous Nitroglycerin on platelet aggregation. It was concluded that increasing doses ofintravenous Nitroglycerin profoundly and dose-dependently inhibit platelet aggregation. This inhibitory effect correlates with glyceryl dinitrate formation.

In this study, the mean heart rates in Group-D and Group-N for the entire duration of surgery were 60.61±4.49 & 95.58±9.41 respectively. There was statistically significant difference between the two groups regarding pulse rates. The mean systolic blood pressures in Group-D and Group-N for the entire duration of surgery were 92.73±8.58 & 91.86±8.77 respectively. There was no statistically significant difference between the two groups regarding systolic blood pressures. The mean diastolic blood pressures in Group-D and Group-N for the entire duration of surgery were 58.40±7.03 & 58.33±7.48 respectively. There was no statistically significant difference between the two groups regarding diastolic blood pressures. The mean arterial pressures in Group-D and Group-N for the entire duration of surgery were 69.85±7.47 & 69.54±7.91 respectively. There was no statistically significant difference between the two groups regarding mean arterial pressures. This suggests that both the drug groups are good for achieving controlled hypotensive anaesthesia in endoscopic resection of nasopharyngeal fibroangioma. The mean blood loss in Group-D & Group-N for the entire duration of surgery was 310.71±140.58 ml & 482±141.42 ml respectively.The mean blood loss in Group D was less than the average blood loss in Group N. The difference in blood loss between both the groups was considered to be statistically significant. Infusion of the hypotensive agent was stopped 10 minutes before the anticipated end of surgery. The average blood loss was more with Nitroglycerin when compared to dexmedetomidine. This can be due to increased heart rate caused by Nitroglycerin that is partially offsetting the beneficial effects of hypotension & prolongation of bleeding time by NTG due to inhibition of platelet aggregation because similar decrease in mean arterial pressure was achieved by both the drugs. Dexmedetomidine, on the other hand is an alpha-2 receptor agonist with central sympatholytic action similar to clonidine. This results in decreased in both systemic blood pressure and heart rate.

Conclusion

- Endoscopic removal of Nasopharyngeal Fibroangioma under controlled hypotension technique- Provided a clear field of vision for endoscopic surgery.
- There was no statistically significant difference between the two groups regarding mean arterial pressures.
- Both Nitroglycerine and Dexmedetomidine can be used safely for maintaining hypotensive anaesthesia to achieve a target mean arterial pressure around 60-70 mm/Hg.
- There was statistically significant difference between the two drug groups regarding variations in pulse rate.
- The average blood loss was more with Nitroglycerin when compared to dexmedetomidine.
- Dexmedetomidine is superior to Nitroglycerin in relation to reduction in blood loss during the resection. Dexmedetomidine improved the perioperative hemodynamic stability & causeed controlled hypotension by its central & peripheral sympatholytic action and has got inherent analgesic, sedative and anaesthetic sparing properties which avoids administration of multiple drugs and there side effects.

References

1. Gaillard AL, Anastácio VM, Piatto VB, et al.

A seven-year experience with patients with juvenile nasopharyngeal angiofibroma. Braz J Otorhinolaryngol. 2010;76(2):245-50.

2. Renkonen S, Hagström J, Vuola J, et al. The changing surgical management of juvenile nasopharyngeal angiofibroma. Eur Arch Otorhinolaryngol. 2011; 268(4):599-607.
3. Morgan GE, Mikhail MS, Murray MJ, Hypotensive agents, in: Clinical Anesthesiology, 4 (New Delhi: Tata McGraw-Hill, 2012.pp.255-62.
4. Testa LD, Tobias JD, Pharmacologic drugs for controlled hypotension, J of Clin Anesth. 1995;7:326-37.
5. Kaur M, Singh PM. Current role of dexmedetomidine in clinical anesthesia and intensive care, Anesthesia: Essays and Res. 2011;5(2):128-33.
6. Basar H, Akpinar S, Doganci N, Buyukkocak U, Kaymak C, Sert O. The effect of preanaesthetic single dose dexmedetomidine on induction, hemodynamic and cardiovascular parameters. J ClinAnesth. 2008;20:431-6.
7. Gurbet A, Basagan-Mogol E, Turker G, Ugun F, Kaya FN, Ozcan B. Intraoperative infusion of dexmedetomidine reduces perioperative analgesic requirements. Can J Anesth. 2006;53:646-52.
8. Guo TZ, Jiang JY, Buttermann AE, Maze M. Dexmedetomidine injection into the locus coeruleus produces antinociception. Anesthesiology. 1996; 84:873- 81.
9. Ulger MH, Demirbilek S, Koroglu A, Borazan H, Erosy MO. Orta kulak cerrahsindedekmedetomid in ilekontro lie hip otansiyon. Inonu Uni Tip KakDerg 2004;11:237-41.
10. Peden CJ, et al. The effect of intravenous Dexmedetomidine premedication on the dose equirement of propofol to induce loss of consciousness in patients receiving alfentanil. Anaesthesia. 2001:56(5):408-13.
11. Guven DG, Demiraran Y, Sezen G, Kepek O, Iskender A. Evaluation of outcomes in patients given dexmedetomidine in functional endoscopic sinus surgery. Ann Otol Rhinol Laryngol. 2011; 120:586–92.
12. Goksu S, Arik H, Demiryurek S, Mumbuc S, Oner U, Demiryurek AT. Effects of Dexmedetomidine infusion in patients undergoing functional endoscopic sinus surgery under local anaesthesia. Eur J Anaesthesiol. 2008;25:22–28.
13. Karl- Erik Karlberg et al. Dose-dependent effect of intravenous Nitroglycerin on platelet aggregation, and correlation with plasma glyceryl di nitrate concentration in healthy men. American Journal of Cardiology, 1992:69(8):802-05.

STATEMENT ABOUT OWNERSHIP AND OTHER PARTICULARS

"Indian Journal of Anesthesia and Analgesia " (See Rule 8)

1.	Place of Publication	:	Delhi
2.	Periodicity of Publication	:	Quarterly
3.	Printer's Name	:	**Asharfi Lal**
	Nationality	:	Indian
	Address	:	3/258-259, Trilok Puri, Delhi-91
4.	Publisher's Name	:	**Asharfi Lal**
	Nationality	:	Indian
	Address	:	3/258-259, Trilok Puri, Delhi-91
5	Editor's Name	:	**Asharfi Lal** (Editor-in-Chief)
	Nationality	:	Indian
	Address	:	3/258-259, Trilok Puri, Delhi-91
6.	Name & Address of Individuals who own the newspaper and particulars of shareholders holding more than one per cent of the total capital	:	**Asharfi Lal** 3/258-259, Trilok Puri, Delhi-91

I Asharfi Lal, hereby declare that the particulars given above are true to the best of my knowledge and belief.

Sd/-

(Asharfi Lal)

Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(1) (Part - II): 219-226
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.31

Effect of Chronic Exposure to Trace Anaesthetic Gases on Plasma Homocysteine levels in Operating Room Personnel

Adam Amararapu[1], Nagaraj Gajagouni[2], Manasa Surampalli[3]

[1]Associate Professor, [2]Assistant Professor, [3]Post Graduate, Dept. of Anesthesia, MNR Medical College and Hospital, Sangareddy District, Telangana 502285, India.

Abstract

Introduction: A growing body of evidence indicates that Homocysteine acutely rises as a side effect of exposure to Nitrous oxide during surgery in adults. Under normal conditions, Homocysteine is remethylated back to Methionine by the enzyme Methionine synthase which requires the reduced form of Vitamin B12 as a coenzyme and 5-Methyltetrahydrofolate as the methyl donor. Exposure to N_2O inhealthcare workers is associated with alterations of Vitamin B12 metabolic status. *Aim:* To find the Effect of Chronic Exposure to Trace Anaesthetic Gases on Plasma Homocysteine levels in Operating Room Personnel. Objective of my study is to find plasma Homocysteine levels in operating room personnel compared to non exposed. *Materials and Methods:* This study is conducted on 60 personnel. A total of 30 subjects exposed to waste Anaesthetic gases for a minimum of 5 years in unscavenged operation theatres and also 30 controls who were not exposed to Anaesthetic gases were selected at random to compare. From all the cases and controls detailed information pertaining to various epidemiological parameters and evaluated the level of serum Homocysteine by using ADVIA Centaur and ADVIA Centaur XP systems. *Results:* Mean Homocysteine value in over all analysis OT exposed group is 13.285 µmol/L and in controls is 10.545 µmol/L which are not equal. The p-Value of 0.00135 is "statistically significant", there is a difference in the Homocysteine levels between the two groups which is because of an effect of the Anaesthetic gas exposure. *Conclusion:* Subjects in the exposed group are distributed in the Homocysteine values of >12 µmol/L while the subjects in the control group are distributed within the Homocysteine value of <12 µmol/L. Statistical analysis showed significant difference in Homocysteine levels between OT exposed and non exposed groups. So we conclude that long term exposure to trace Anaesthetic gases like Nitrous oxide can lead to elevated Homocysteine levels in health care workers.

Keywords: Homocysteine levels; 5-Methyltetrahydrofolate; Nitrous oxide.

How to cite this article:

Adam Amararapu, Nagaraj Gajagouni, Manasa Surampalli. Effect of Chronic Exposure to Trace Anaesthetic Gases on Plasma Homocysteine levels in Operating Room Personnel. Indian J Anesth Analg. 2019;6(1):219-226.

Introduction

Nitrous Oxide was first Synthesized by Joseph Priestly in 1722. Its Psychotropic effects were first appreciated by Humphrey Davy. The first clear association of N_2O and hematologic disease was reported by Lassen et al. in the Lancet in 1956. They studied it prospectively and found that Granulocytopenia developed on the fourth day (with 50% N_2O). A Bonemarrow biopsy was consistent with Pernicious anaemia with Megaloblastic changes. In 1978, Sahenk reported a case of polyneuropathy from recreational Nitrous oxide use and Layzer reported on dentists who

Corresponding Author: Nagaraj Gajagouni, Assistant Professor, Dept. of Anesthesia, MNR Medical College and Hospital, Sangareddy District, Fasalwadi, Telangana 502285, India.

E-mail: nagaraj.gajagouni@gmail.com

Received on 30.10.2018, **Accepted on** 03.12.2018

developed polyneuropathy and it was linked to the deficiency of Vitamin B12. A growing body of evidence indicates that Homocysteine acutely rises as a side effect of exposure to Nitrous oxide during surgery in adults [1]. Homocysteine is an intermediary metabolite in the metabolism of the sulfur-containing amino acids. It is produced by de-methylation of Methionine and is a substrate for synthesis of Cystathionine and then Cysteine. Under normal conditions, Homocysteine is remethylated back to Methionine by the enzyme Methionine synthase which requires the reduced form of Vitamin B12 as a coenzyme and 5-Methyltetrahydrofolate as the methyl donor.

Nitrous oxide irreversibly oxidizes the Cobalt atom of Vitamin B12, inactivating it which is a co-factor for Methionine synthase. Whether this acute effect translates into clinical outcomes of relevance has been the research objective of two recent prospective randomized control trials in adults1-3. In these trials, Nitrous oxide induced acute Hyperhomocysteinemia (>13.4 µmol/L) was associated with increased risk of Myocardial ischemia, and other major post-surgical complications1. Exposure to N_2O inhealthcare workers is associated with alterations of Vitamin B12 metabolic status, theextent of which depends on the level of exposure [4,5]. Some of these studies havedemonstrated a relationship between N_2O exposure and altered Vitamin B12 metabolismand plasma Homocysteine levels. Here, we evaluated the level of serum Homocysteinein personnel exposed to ot atmosphere in Gandhi hospital Secunderabad, and compared with non OT healthy controls by using ADVIA Centaur and ADVIACentaur XP systems.

Materials and Methods

Blood samples are collected according to National Committee for Clinical Laboratory Standards. 5 ml of blood collected in EDTA vaccutainers from an antecubital vein after 6-8 hours of fasting and should not have a high protein meal 6-8 hours before collection from all the subjects who gave their consent to participate in the study after explaining to them the purpose of study. Samples are centrifuged and red blood cells are separated. Speciemens are capped tightly and refrigerated at 2-8^{0}C until testing.

A total of 30 subjects exposed to waste Anaesthetic gases for a minimum of 5 years who routinely provide full-time assistance during operations on a day-to-day basis in operation theatres, who gave their consent to participate in the study are registered to study various epidemiological parameters and to screen for the plasma Homocysteine levels. Obtained the permission from institutional Ethical committee.

Inclusion Criteria

OT Personnel, who are exposed to Anaesthetic gases for >5 years in operation theatres. Also 30 controls who are not exposed to Anaesthetic gases are selected at random to compare with the data generated on the subjects exposed to these gases.

Exclusion Criteria

Age < 20 years and > 65 years, Recent use of vitamins, Pregnancy, Bleeding tendencies, Systemic diseases like liver and renal failure, Clinical signs and symptoms of cobalamine or folate deficiency . Medications known to effect plasma Homocysteine.

From all the cases and controls detailed information pertaining to various epidemiological parameters such as age, sex, history of exposure, other comorbidities are collected using a specific proforma.

Homocysteine testingdone by ADVIA Centaur XP assays use Acridinium ester (AE) as the chemiluminescent label, because AE does not require the addition of a catalyst or substrate. It is easy to automate direct Chemiluminescence using AE and provides many benefits, such as long reagent shelf life, fast reaction time, and assay sensitivity. The ADVIA Centaur XP assays use the dimethyl form of AE because its stability allows long reagent shelf life.

Statistical Analysis

The results are expressed as frequencies or mean values (SD). Differences in demographic characteristics between groups were analysed. Since we are studying the effectiveness of a single variable (Homocysteine Value) on two control groups (With Gas Exposure and Without Gas Exposure) a One-Way ANOVA with a Confidence Interval of 95% (Alpha = 0.05) is used between the subjects. To identify whether our null hypothesis (H0) that the means of the groups are equal or the alternative hypothesis (H1) that the means are not equal we shall look at the results. A p-value of 0.05 or less rejects the null hypothesis that is; the statistical assumptions used imply that only 5% of the time would the supposed statistical process produce a finding this extreme if the null hypothesis were true.

Results

The sample considered for the study included 60 subjects of which 30 subjects were in the exposed group who are exposed to waste Anaesthetic gases in unscavenged OT and 30 subjects were in the control group.

Table 1: Demographic distribution of the exposed group as well as control group

Demogrphic details	Exposed Group: With Gas Exposure	Control Group: Without Gas Exposure	p-Value
Age(in years)	41.9	42.8	0.68966
Males	7(23%)	23(77%)	0.78
Females	8(27%)	22(73%)	
BMI	24.497(6.629)	24.702(7.359)	0.7651
Average duration of exposure in years	14.5 0	0 0	1.95

All the subjects were aged between 28 to 58 years in both the exposed group and control group with a mean age of 41.9 years and 42.8 years respectively. The statistical analysis with a confidence interval of 95% resulted in a p-Value of 0.68 which is considered to be "statistically not significant" as it is greater than the ideal value of 0.05 (A p-value of 0.05 or less rejects the null hypothesis). In terms of the sex distribution of the sample, 23% (7) of the subjects were male and 77% (23) were female in the exposed group and 27% (8) of the subjects were male and 73% (22) were female in the control group. A balanced sample was selected to ensure that there were no statistical differences in the Homocysteine levels based on the sex (Table 1).

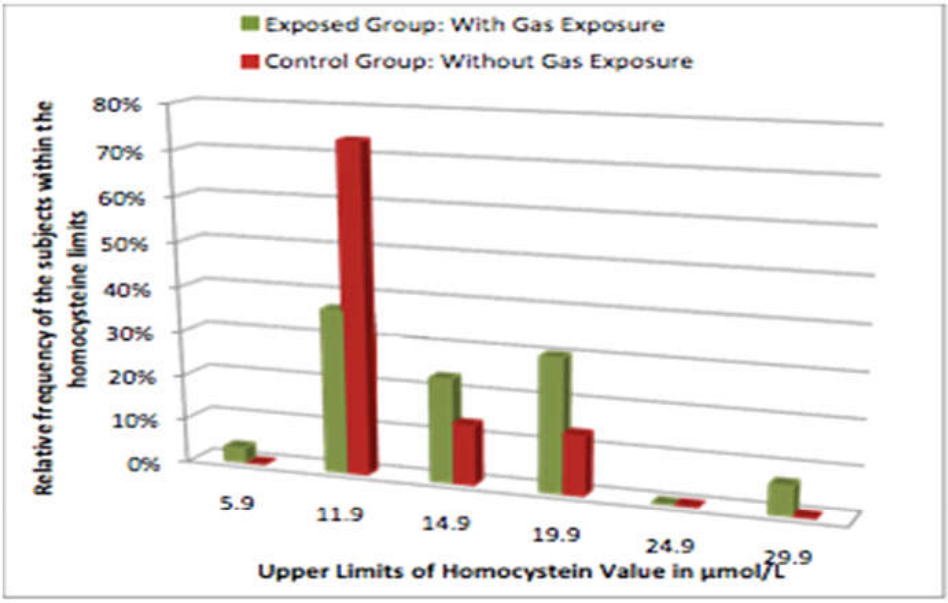
BMI Value resulted in a p Value of 0.76 which is considered to be "statistically not significant". Hence the BMI values of both the groups is equivalent.

To compare the difference between the Homocysteine values in the exposed and control groups, the subjects in the exposed group were exposed to > 5 years of Anaesthetic gas. The mean duration of exposure in OT exposed group is 14.5 years and is observed to be zero in the control group as it is not exposed to any gases. The statistical analysis resulted in a very low p-Value of 1.95E-13 which is considered to be "statistically highly significant". Hence we conclude that there is a difference in the duration of exposure which resulted in a statistical difference in the Homocysteine levels.

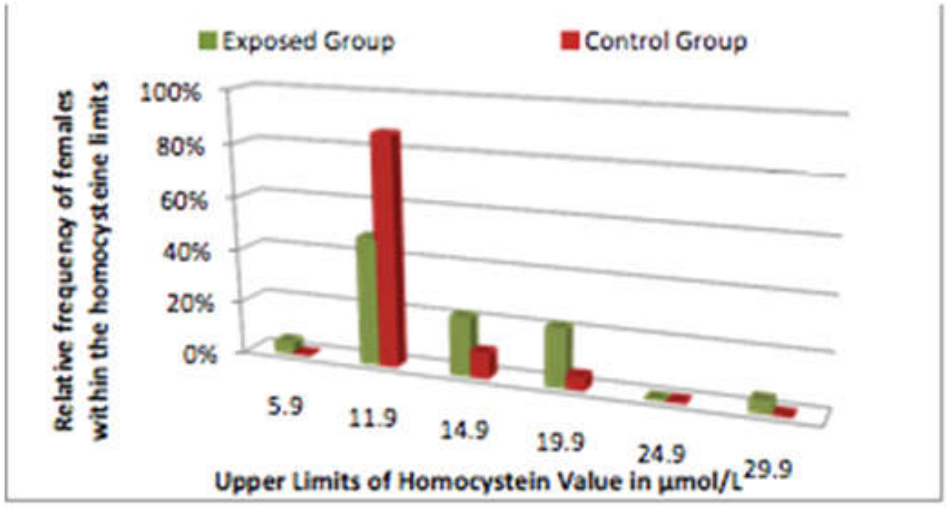
The graph 1 we can observe that the maximum number of subjects in the control group are distributed within the ideal Homocysteine value of < 12 µmol/L while the subjects in the exposed group are distributed in the Homocysteine values of > 12 µmol/L as well (Graph 1).

From the graph 2 we can observe that the number of females in the control group are distributed within the ideal Homocysteine value of < 12 µmol/L while the females in the exposed group are distributed in the Homocysteine values of > 12 µmol/L as well (Graph 2).

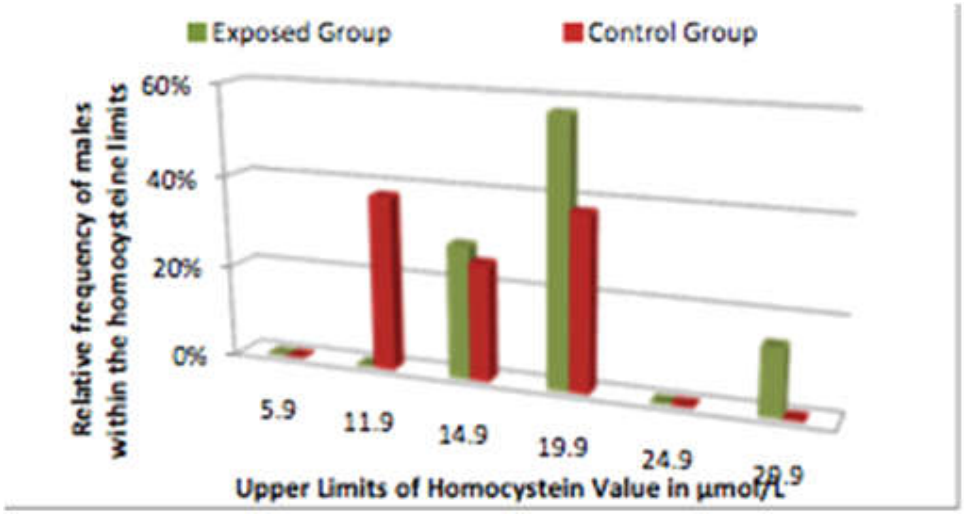
From the graph 3 we can observe that the number of males in the exposed group are distributed within



Graph 1: Distribution of Homocysteine values in the subjects



Graph 2: Distribution of Homocysteine values in female subjects



Graph 3: Distribution of Homocysteine values in male subjects

Table 2: Female and male observation of the mean values of homocysteine

Female Analysis	Homocysteine value (in umol/L)	Age in years	Duration of exposure in years	BMI
Mean values of Exposed Group	12.02956	39.260	12.6956	24.53957
Mean values of Control Group	9.510454545	40.090	0	24.09227
p Value	0.028131938	0.68656	5.46E-11	0.574845
Male analysis				
Mean values of Exposed Group	17.40714286	50.57143	20.42857143	24.35714
Mean values Control Group	13.39125	50.25	0	26.37875
p Value	0.050269817	0.946344	9.94E-05	
Over analysis				
Mean values of Exposed Group	13.28433333	41.9	14.5	24.497
Mean values of Control Group	10.54533333	42.8	0	24.702
p Value	0.01353611	0.6897	1.95E-13	0.7651

the Homocysteine value of >12 µmol/L (Graph 3).

Mean Homocysteine value in females OT exposed group is 12.029 µmol/L and in controls is 9.51 µmol/L. The p-Value of 0.0281 is "statistically significant" ($p < 0.05$) and hence concluding that there is a difference in the Homocysteine levels between the two groups which is because of an effect of the Anaesthetic gas exposure (Table 2).

Mean Homocysteine value in males OT exposed group is 17.408 µmol/L and in controls is 13.392 µmol/L which are not equal. The p-Value of 0.00502 is "statistically significant" and hence we conclude that there is a difference in the Homocysteine levels between the two groups which is because of an effect of the Anaesthetic gas exposure.

Mean homocysteine value inover all analysis OT exposed group is 13.285 µmol/L and in controls is 10.545 µmol/L which are not equal. The P-Value of 0.00135 is "statistically significant", and hence concluding that there is a difference in the Homocysteine levels between the two groups which is because of an effect of the Anaesthetic gas exposure.

Discussion

There are many trails indicating that exposure to Nitrous oxide during surgery in adults causes raise in Homocysteine levels during post operative period 1-3. The first clear association of N2O and hematologic disease was reported by Lassen et al in the Lancet in 1956. They found that Granulocytopenia was developed on the fourth day (with 50% N_2O) and Bonemarrow biopsy was consistent with Pernicious anaemia with Megaloblastic changes. Homocysteine is produced by demethylation of Methionine [3]. Under normal conditions, Homocysteine is remethylated to Methionine by the enzyme Methionine synthase and this requires the reduced form of vitamin B12 as a coenzyme and 5-methyltetrahydrofolate as the methyl donor 36. Nitrous oxide irreversibly oxidizes the Cobalt atom of vitamin B12. This leads to inactivation of vitamin B12, which is a co-factor for Methionine synthase. Whether this acute effect has relevant clinical outcome, has been the research objective of two recent prospective trials in adults [1,2]. In these studies, there is Nitrous oxide induced acute Hyperhomocysteinemia (>13.4 µmol/L) and this was associated with increased risk of major post-surgical complications. Paul S. Myles, Chan MT et al. [4] study showed there is significant increase in postoperative Homocysteine in N_2O exposed group. There was also decrease in flow-mediated dilatation in N_2O exposed group. Endothelial function in patients undergoing noncardiac surgery was significantly impaired. N_2O exposure could be a risk factor for postoperative cardiovascular morbidity [1]. Badner NH et al. [1] study found a significant increase in Homocysteine levels with N_2O administration in patients undergoing Carotid endarterectomy and these patients were associated with increased postoperative myocardial ischemia. There is an assosciation between exposure to N_2O and alteration of vitamin B12 metabolic status in healthcare workers and the extent of alteration depends on the level of exposure. Some of these studies have demonstrated a relationship between N_2O exposure and altered vitamin B12 metabolism and plasma Homocysteine levels.

The aim of our study is to find the effect of chronic exposure to trace anaesthetic gases on plasma Homocysteine levels in operating room personnel.

Subjects

Our study design included 30 subjects who are exposed to gases and 30 controls who are not exposed. In the present study subjects in the 2 groups did not vary much with respect to age, sex and BMI. In terms of sex distribution of the sample, 23% (7) of the subjects were male and 77% (23) were female in the exposed group and 27% (8) of the subjects were male and 73% (22) were female in the control group. In our study a balanced sample was selected to ensure that there was no statistical difference in Homocysteine levels based on the sex. Comparing the current study with that of W. Krajewski, M. Kucharska, et al. study which included only females (95) in study group and only females (90) in control group [5].

In the present study all the subjects were aged between 28 to 58 years in both the exposed group and control group with a mean age of 41.9 years and 42.8 years respectively. The similarity ensures that there is no statistical difference in the Homocysteine levels based on the age. W. Krajewski, M. Kucharska, et al. [5] study included subjects aged between 25 and 56 years. 5 Mean BMI Value in our study is 24.4 and 24.7 respectively in exposed group and control group. BMI values of both the groups is equivalent.

To compare the difference between the Homocysteine values in the exposed and control groups, the subjects were exposed to > 5 years

to Anaesthetic gases in one group. The subjects in exposed group are fulltime doctors and nurses working in OTs. The mean duration of exposure in OT exposed group is 14.5 years and it is zero in thecontrol group as it is not exposed to any Anaesthetic gases. There is a difference in theduration of exposure which resulted in a statistical difference in the Homocysteinelevels. Nitrous oxide reacts with the cobalamin corrin nucleus oxidizing the cobalt atom. So themolecule loses its power to form a carbon-cobalt bond with the methyl ligand [6]. Thus, Nitrous oxide prevents the formation of Methylcobalamin and inactivates circulating Methionine synthase. Nitrous oxide induced inactivation of Methylcobalamin isirreversible in animal and human tissues since only bacteria possess the enzymes torevert the oxidative damage to cobalamin. Therefore, recovery of Methionine synthaseactivity requires replenishment of cobalamin (I). Waclawik AJ et al. [7] described a case of Myeloneuropathy from Nitrous oxide abuse.

Following parenteral B12 administration, his neurological deficit resolved and B12 and MMA levels normalized, but Homocysteine level is elevated. After halting N_2O exposure patients Homocysteine level normalized [12] Because of interassay variability leading to method dependent normal ranges, tHcyconcentration of 12 µmol/litre reflecting 95th percentile value in the control group wastaken in this study as a cut-off value discriminating between elevated and normal tHcylevels.

In our study the mean value of Homocysteine is 13.285 µmol/L and 10.546 µmol/L in the exposed and control group respectively. The statistical analysis resulted in a P-Value of 0.0135 (confidence interval of 95%). This implies that the difference is statistically significant. In W. Krajewski, M. Kucharska et al. [5] study, subjects exposed to N2O presented with lower Vitamin B12 [372.8 (12.1) vs 436.8 (13.2) pmol litre, p = 0.001] and higher tHcy. [11.2 (0.5) vs 8.9 (0.5) mmol litre, p¼=0.006]. The changes in Vitamin B12 status were aggravated in subjects exposed to N_2O in concentrations substantially exceeding occupational exposure limit. Observations in present study are in accordance with the W. Krajewski et al. study [5]. The reason for increase in Homocysteine levels is, Nitrous oxide by oxidizing vitamin B12 and inactivating Methionine synthase. In patients exposed to Nitrous oxide there is inactivation of Vitamin B12 leading to increased circulating levels of Folates and Homocysteine.

Subjects in the exposed group are distributed in the Homocysteine values of >12 µmol/L while the subjects in the control group are distributed within the Homocysteine value of <12 µmol/L. Mean Homocysteine value in Females in OT exposed group is 12.029 µmol/L and in controls is 9.51 µmol/L, which are not equal. Mean Homocysteine value in Males in OT exposed group is 17.408 µmol/L and in controls is 13.392 µmol/L, which are not equal. There is a difference in the Homocysteine levels between the two groups. Chronic Hyperhomocysteinemia is concurrent with ischemic heart disease (coronary heart disease, myocardial infarction), and cerebrovascular disease, (fatal and hemorrhagic stroke) [8]. Whether this assosciation is due to pathogenic effect of Homocysteine (causational) or increased levels is an assosciated marker, remains controversial.

ENIGMA (Evaluation of Nitrous oxide In the Gas Mixture for Anesthesia) trial showed there is a pathophysiologic rationale for increased long-term cardiovascular morbidity and mortality in patients receiving Nitrous oxide. Post surgery Homocysteine concentrations were ≥13.5 µmol/L in these adults and these were also associated with an increased risk of major complications and cardiovascular events [9].

There is generation of reactive oxygen species like Superoxide anions (O^{2-}) and Hydrogen peroxide (H_2O_2), with high Homocyteine levels, since these originate from the auto-oxidation of Homocysteine. Reactive oxygen species promote loss of membrane function and increased membrane permeability (lipid peroxidation). Either the decreased production of Nitric oxide, or the increased formation of superoxide, or both may result in endothelial cell dysfunction. These observations are in accordance with the following Literature. W. Krajewski, M. Kucharska, et al. [5] study on Impaired vitamin B12 metabolic status in healthcare workers exposed to Nitrous oxide showed no significant differences in Haematological parameters and folic acid between both the groups. However, subjects exposed to N_2O presented with lower vitamin B12. The changes in vitamin B12 status was aggravated in subjects exposed to N_2O in concentrations exceeding occupational exposure limit. N_2O exposure level and vitamin B12 concentration showed significant negative correlation and N_2O exposure level and tHcy concentration showed a significant positive correlation. N_2O exposed subjects with various vitamin B12 concentrations have Abnormal tHcy concentrations.

Sharer et al. [10] studied the Effects of chronic

exposure to Nitrous oxide on Methionine synthase activity. A 24 hour exposure to concentrations of ≤ 860 parts per million (ppm) N_2O showed no change in Methionine synthase function in Sprague-Dawley rats. However, at anesthetic concentrations, Methionine synthase activity is inhibited rapidly in rats. In Koblin study on Inactivation of Methionine synthase by Nitrous oxide in mice demonstrated that N_2O (70%) inhibited Methionine synthase activity in Liver biopsies with a 50% reduction in activity predicted after approximately 1.5 hour. Consistent with this effect, the duration of N_2O exposure is correlated with increased Homocysteine levels. 5,10-Methylenetetrahydrofolate reductase (MTHFR), also plays an important role in the conversion of Homocysteine to Methionine by generating 5-methyltetrahydrofolate [11]. Waclawik AJ et al. [7] described a case of Myeloneuropathy from Nitrous oxide abuse. A Nitrous oxide abuse patient developed diffuse paresthesias and sensory loss and mildly reduced serum vitamin B12 concentration with high levels of Methylmalonic acid (MMA) and Homocysteine. There was no evidence of B12 malabsorption in this patient. Following parenteral B12 administration, his neurological deficit resolved and B12 and MMA levels normalized, but Homocysteine level is elevated. After halting N_2O exposure patients Homocysteine level normalized. This demonstrates the importance of serum Homocysteine level measurements in cases of suspected N_2O toxicity.

In Doran et al. [12] study on Toxicity after intermittent inhalation of Nitrous oxide for analgesia noted Nitrous oxide abusers present with altered mental status, paresthesias, ataxia, and weakness and spasticity of the legs. Tsung-Ta Chiang et al. [13] described a case of Recreational Nitrous Oxide Abuse Induced Vitamin B12 Deficiency. This patient presented with skin pigmentation over the dorsum of fingers, toes, and trunk, and Myeloneuropathy of the posterior and lateral columns. Low serum vitamin B12 level and an elevated serum Homocysteine level were present. Patients history revealed N_2O exposure. Only Symptoms improved significantly with vitamin B12 treatment. Methyl group from N5-methyltetrahydrofolate is transferred to Homocysteine by Methionine synthase producing Tetrahydrofolate and Methionine. In humans, inhibition of Methionine synthase results in the development of Megaloblastic anemia, and eventually Subacute combined degeneration of the spinal cord.

Repeated occupational exposure to N_2O may disturb vitamin B12 metabolic status. N_2O preferentially targets metabolically active cobalamin (I). So decreased levels of vitamin B12 were reported in N_2O abusers and sporadically during N2O anaesthesia. Several studies demonstrated that intraoperative exposure to N_2O is associated with postoperative increases in plasma tHcy [1-3]. In the present study, we extend these observations to operating theatre personnel under repeated occupational exposure to N_2O. Theoretically, in healthcare workers active under excessive occupational exposure to N_2O, disturbances of vitamin B12 metabolism were evident. They might be more susceptible to development of vitamin B12 deficiency symptoms under certain conditions such as dietary vitamin B12 restriction. Moreover, they are likely to develop Hyperhomocysteinaemia, and it is a well-recognized independent risk factor for Arterial and Venous thrombosis and Coronary heart disease. Our study was in contrast with following Literature. Gudrun Abascall et al. [14] studied whether routine blood test is of value, for evaluating effects among midwives working with Nitrous oxide for pain relief in delivery unit. The study was done to determine if work place ambient air Nitrous oxide exposure resultsin detectable Hyperhomocysteinemia or signs of Macrocytocis in midwives. One of 3 delivery units ambient air quality measures exceeded recommended ranges. There were no signs of routine blood test pathology in the personnel studied.

All the personnel in the present study are exposed continuously to trace gases in OTs unlike the midwives.

M Salo et al. [15] study on signs of vitamin B12 - Nitrous oxide interaction in operating theatre personnel showed no changes in the peripheral blood samples. Peripheral blood counts and films, serum vitamin B12 and plasma and erythrocyte folate concentrations were studied in eight anaesthetists and seven internists to find if the interaction is an occupational health hazard to operating theatre personnel chronically exposed to trace concentrations of Nitrous oxide. In addition, blood counts were studied in two retrospective materials of 118 operating theatre nurses working in scavenged operating theatres and in ten subjects working in unscavenged theatres. No definite signs of B12- nitrous oxide interaction could be observed in the peripheral blood samples from these persons. Number of subjects in the exposed group in the present study are 30 compared to the above study and even in this present study 12 out of 30 subjects in the exposed group showed elevated Homocysteine levels. Koblin et al. [11]. study on the of Effect of Nitrous oxide on Folate and vitamin B12 metabolism in patients did not find any changes in

formic acid and formimino glutamicacid urinary excretion after 3 hour of Nitrous oxide exposure during hip replacement inelderly patients. Formic acid and formimino glutamic acid urinary excretion are markers of Methionine synthase function. In younger patients undergoing longer surgery a minorincrease in these markers was found. Whether the elderly represent a vulnerable population to Nitrous oxide induced Methionine synthase inhibition needs further investigation. Care should be taken with folate or cobalamin deficient patients [60]. In 1990 another study by Waldman et al. [16]. on Hematologic effects of Nitrous oxide in surgical patients did not find hematologic abnormalities in orthopedic and neurosurgical patients exposed to Nitrous oxide, apart from a smaller perioperative increase in Leukocyte count [61].

Conclusion

Based on the present study, we conclude that there are Health Effects on OT personnel on Chronic Exposure to Trace Anaesthetic Gases. Our sample size was comparable in terms of age, sex, BMI. Subjects in the exposed group are distributed in the Homocysteine values of > 12 µmol/L while the subjects in the control group are distributed within the Homocysteine value of < 12 µmol/L. Statistical analysis showed significant difference in Homocysteine levels between OT exposed and non exposed groups. So we conclude that long term exposure to trace Anaesthetic gases like Nitrous oxide can lead to elevated Homocysteine levels in health care workers.

References

1. Badner NH, Drader K, Freeman D, Spence JD. The use of intraoperative nitrous oxide leads to postoperative elevations in plasma homocysteine. AnesthAnalg. 1998;87:711–3.
2. McNeely JK, Buczulinski B, Rosner DR: Severe neurological impairment in an infant after nitrous oxide anesthesia. Anesthesiology. 2000;93:1549–50.
3. Brosnan JT, Brosnan ME. The sulfur-containing amino acids: an overview. J Nutr 2006;136:1636S-1640.
4. Myles PS, Chan MT, Leslie K, Peyton P, Paech M, Forbes A. Effect of nitrous oxide on plasma homocysteine and folate in patients undergoing major surgery. Br .J Anaesth. 2008 Jun;100(6):780-6.
5. W. Krajewski, M. Kucharska, B. Pilacik, M. Fobker, J. Stetkiewicz, J.R. Noferand T. WronskaNofer: Impaired vitamin B12 metabolic status in healthcare workers occupationally exposed to nitrous oxide British Journal of Anaesthesia 2007;99(6):812–18.
6. Royston BD, Nunn JF, Weinbren HK, Royston D, Cormack RS. Rate of inactivation of human and rodent hepatic methionine synthase by nitrous oxide. Anesthesiology. 1988;68:213-6.
7. Waclawik AJ, Luzzio CC, Juhasz-Pocsine K, Hamilton V. Myeloneuropathy from nitrous oxide abuse: unusually high methylmalonic acid and homocysteine levels. WMJ. 2003;102(4):43-5.
8. Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. JAMA. 2002 Oct 23-30;288(16):2015-22.
9. Leslie K, Myles PS, Chan MT, Forbes A, Paech MJ, Peyton P, Silbert BS, Williamson E. Nitrous oxide and long-term morbidity and mortality in the ENIGMA trial. AnesthAnalg. 2011 Feb;112(2):387-93.
10. Sharer NM, Nunn JF, Royston JP, Chanarin I. Effects of chronic exposure to nitrous oxide on methionine synthase activity. Br J Anaesth 1983; 55:693–701.
11. Koblin DD, Watson JE, Deady JE, Stokstad EL, Eger EI II. Inactivation of methionine synthetase by nitrous oxide in mice. Anesthesiology. 1981; 54:324–35.
12. Doran M, Rassam SS, Jones LM, Underhill S. Toxicity after intermittent inhalation of nitrous oxide for analgesia. BMJ. 2004; 328:1364–5.
13. Tsung-Ta Chiang, Chih-Tsung Hung, Wei-Ming Wang, Jiunn-Tay Lee, Fu-Chi Yang. Recreational Nitrous Oxide Abuse- Induced Vitamin B12 Deficiency in a Patient Presenting with Hyperpigmentation of the Skin. Case Rep Dermatol 2013;5:186–91.
14. Gudrun Abascall, Maud Johansson, JanJakobsson. Is routine blood test of value for evaluating health effects among midwives working with nitrous oxide for pain relief in delivery unit. 2011;3(3):162-65.
15. M Salo A Rajamäki J Nikoskelainen. Absence of signs of vitamin B12-nitrous oxide interaction in operating theatre personnel. ActaAnaesthesiologic aScandinavica. 1984 March;28(1):106-8.
16. Waldman FM, Koblin DD, Lampe GH, Wauk LZ, Eger EI II: Hematologic effects of nitrous oxide in surgical patients. AnesthAnalg. 1990;71:618–24.

Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(1) (Part - II): 227-233
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.32

A Clinical Comparative Study between Caudal Levobupivacaine-Clonidine and Ropivacaine- Clonidine for Postoperative Analgesia in Paediatric Subumbilical Surgeries

Aiyappa DS[1], Janardhanan G[2], Pavitra Pushpa[3]

[1]Assistant Professor [3]Senior Resident, Department of Anaesthesiology, K.V.G. Medical College and Hospital, Sullia, Karnataka 574327, India. [2]Associate Professor, Department of Anaesthesiology, Kodagu Institute of Medical Sciences, Madikeri, Karnataka 571201, India.

Abstract

Context: The use of clonidine as adjuvant to newer anaesthetic agents like levobupivacaine or ropivacaine in caudal block enhance postoperative analgesia. *Aims:* the purpose of the study was to compare the efficacy of levobupivacaine 0.25% with clonidine 1 mcg/kg to that of ropivacaine 0.25% with clonidine 1 mcg/kg with respect to post-operative analgesia following caudal administration in children. *Settings and Design:* Prospective, double blinded, randomized controlled trial. *Materials and Methods:* sixty children aged 2-6 years, of American Society of Anesthesiologists (ASA) physical status I or II, undergoing subumbilical surgeries were randomly allocated to two groups. After induction with general anaesthesia, Group L received 1 ml/kg of 0.25% levobupivacaine with clonidine 1 mcg/kg and Group R received 1 ml/kg of 0.25% ropivacaine with clonidine 1 mcg/kg caudally. Duration of analgesia (primary outcome), pain scores, number of rescue analgesic doses and side effects if any were recorded. *Statistical analysis used:* All the results were tabulated and analysed statistically. After checking for normality assumption, Student's t test was used for numerical data and Chi-square test for categorical data. p values<0.05 were considered significant. *Results:* Groups were comparable with respect to age, weight, sex, type and duration of surgery. Mean duration of analgesia in Group L was 11.05±0.26 versus 10.86±0.22 hours in Group R, hence comparable between the two groups. None of the groups had nausea, vomiting, bradycardia or hypotension and no significant sedation was noted. *Conclusion:* Clonidine(1 mcg/kg) when used as an adjuvant in caudal block along with either levobupivacaine 0.25% or ropivacaine 0.25% produces similar post-operative analgesia with fewer side effects.

Keywords: Levobupivacaine; Ropivacaine; Clonidine; Caudal block; CHIPPS score.

How to cite this article:

Aiyappa D S, Janardhanan G, Pavitra Pushpa. A Clinical Comparative Study between Caudal Levobupivacaine-Clonidine and Ropivacaine-Clonidine for Postoperative Analgesia in Paediatric Subumbilical Surgeries. Indian J Anesth Analg. 2019;6(1):227-33.

Introduction

Caudal block is one of the simplest and safe technique used for surgical anaesthesia in children undergoing subumbilical surgery. It provides excellent pain relief with minimum side effects. As children are not cooperative, caudal block is usually administered in combination with general anaesthesia. This makes detection of early symptoms of systemic toxicity due to accidental intravascular injection of local anaesthetics extremely difficult [6].

Bupivacaine is the most commonly used local anaesthetic agent. It is a racemic mixture of R and S enantiomers, of which R enantiomer is cardiotoxic. Newer local anaesthetics like levobupivacaine and

Corresponding Author: Janardhanan G, Associate Professor, Department of Anaesthesiology, Kodagu Institute of Medical Sciences, Madikeri, Karnataka 571201, India.

E-mail: drjanardhanang@gmail.com

Received on 20.11.2018, **Accepted on** 13.12.2018

ropivacaine are S-enantiomers, which provide wider margin of safety by reducing the occurrence of cardiotoxicity and neurotoxicity [4].

Usage of local anaesthetic agent alone in caudal block provides shorter duration of analgesia. Prolongation of analgesia can be achieved by the addition of various adjutants and amongst them opioids are most widely used. Strict regulations on opioid use (in India) [17] and unpleasant side effects (respiratory depression) [10] has compelled the clinician to use non opioid drugs. Clonidine, an alpha 2 adrenergic agonist produces analgesia without significant respiratory depression [20]. Previous studies have demonstrated that when clonidine was used as an additive to levobupivacaine and ropivacaine in paediatric patients, resulted in prolongation of duration of analgesia significantly [11,16].

To the best of our knowledge, there have been no studies published, comparing levobupivacaine with clonidine and ropivacaine with clonidine for caudal analgesia in paediatric population. The primary aim of this prospective, randomized, double blinded study was to compare the duration of analgesia and secondary aim to measure the number of rescue analgesic doses and any side effects.

Materials and Methods

Following due permission from the Hospital Ethics Committee and written informed consent from parents, this, randomized, double-blinded clinical study was conducted on 60 paediatric patients, aged 2-6 years, of either sex and American Society of Anesthesiologists (ASA) physical status I or II, undergoing subumbilical surgeries (inguinal hernia repair or orchidopexy). Children with history of developmental delay or mental retardation, neurological disorders, pre-existing bleeding disorders, cardiac diseases, sacral abnormalities, infection at caudal injection site and hypersensitivity to local anaesthetic (amide) drugs were excluded from the study.

A pre-anaesthesia evaluation was done day before the surgery, anaesthetic technique and perioperative course were explained to the parents. Patients were randomly allocated to one of the two groups (30 in each) by computer-generated random list which were delivered in sequentially numbered opaque sealed envelopes.

Group L: Received caudal mixture of 1 ml/kg Levobupivacaine 0.25% with preservative free Clonidine 1 mcg/kg.

Group R: Received caudal mixture of 1 ml/kg Ropivacaine 0.25% with preservative free Clonidine 1 mcg/kg.

The investigator who open the sealed envelope, prepared the solutions for caudal administration as per the group mentioned and labelled it as caudal solution without revealing the group or drug. Further he was not involved in the follow-up of the study. Another investigator, who is not aware of the composition of the caudal solution, performed the caudal block and recorded the observations intra operatively.

In our institute, all paediatric patients had intravenous access secured on the previous day of surgery. On the day of surgery, in the preoperative room, patients were re-examined, nil per oral status was confirmed and baseline vitals were recorded. An infusion of Ringer Lactate was started, midazolam (50 mcg/kg) and glycopyrrolate (5 mcg/kg) were given intravenously. Patients were then shifted to operating room, multiparameter monitor were attached and induction of general anaesthesia was done with fentanyl (1 mcg/kg intravenous), propofol (2.5 mg/kg intravenous) and an appropriate size I gel was inserted. Anaesthesia was maintained with mixture of oxygen and air (50:50) and sevoflurane was adjusted to maintain an end-tidal concentration of 1.5–2%, based on intraoperative haemodynamics. Patients were then placed in the lateral position and under all aseptic precautions caudal block was performed using a short bevelled 23G needle. Needle position was confirmed by the characteristic 'pop' sensed during penetration of sacrococcygeal ligament, followed by "whoosh" test (using 0.5 ml of air) as per our institutional practice. After negative aspiration for blood and cerebrospinal fluid, the study drug prepared was injected caudally and the time was noted. All the blocks were performed by same anaesthesiologist throughout the study. The surgical incision was made 15 minutes after caudal placement of the drug. Gross movements or any intraoperative increase in heart rate or mean arterial pressure by more than 15% after 15 minutes of caudal block was defined as inadequate analgesia and additional dose of intravenous fentanyl 1 mcg/kg was given. The intraoperative hemodynamic and respiratory parameters were monitored and documented every 5 min till awakening. The duration of surgery and anaesthesia were noted. At the end of the surgery, inhalation agent was discontinued. I gel was removed, once the children were sufficiently awake. They were then shifted to post- anaesthesia care unit (PACU) for continuous monitoring. Heart rate, mean arterial pressure, SpO_2 (oxygen

saturation), post operative pain status and side effects were recorded by blinded observer (Senior Resident) every 15 minutes for first two hours, every 30 minutes for next four hours and thereafter hourly till 24 hours. Post operative pain status was assessed using Child and Infant post-operative Pain scale (CHIPPS) Score 3 [Table 1]. The degree of sedation was graded using University of Michigan Sedation scale (UMSS) 14 and was assessed every 15 minutes for first 2 hours only.

The primary outcome of the study i.e. the duration of analgesia (the time duration from caudal placement of drug until the requirement of first rescue analgesia) was recorded. Rescue analgesia was given with intravenous paracetamol 15 mg/kg, when CHIPPS score was ≥ 4. Secondary outcome such as the number of rescue analgesic doses required for first 24 hours, adverse effects like post operative nausea and vomiting, respiratory depression (a decrease in SpO_2 to < 92% requiring supplemental oxygen), hypotension (fall in mean arterial blood pressure > 20% of the baseline value) and bradycardia (fall in heart rate > 20% of the baseline value) were recorded. Next day the patients were discharged and the parents were given phone numbers to inform any untoward incidents.

Based on the pilot study, sample size was determined using Open EPI software. The mean duration of analgesia expected for levobupivacaine – clonidine and ropivacaine – clonidine group were 11.05±0.26 and 10.86±0.22 hours respectively. This indicated a sample size of 26 subjects would be required in each group at an alpha error of 0.05 and power of 80%. We, therefore recruited 30 patients in each group. Statistical analysis was performed using the statistical package SPSSv19.0 [IBM India Pvt Ltd, Bangalore, India]. The categorical data were represented as numbers and percentages and numerical data were represented as mean and standard deviation. The data collected were analysed for normal distribution by one-way analysis (and were normally distributed). Student's t-test was used for Numerical data and Chi-square test for categorical data. Significance was defined as p value<0.05.

Table 1: Children and Infants Post-operative Pain Scale (CHIPPS)

CHIPPS score		
Item	**Response**	**Score**
Crying	None	0
	Moaning	1
	Screaming	2
Facial expression	Relaxed/smiling	0
	Wry mouth	1
	Grimace (mouth and eyes)	2
Posture of the trunk	Neutral	0
	Variable	1
	Rear up	2
Posture of the legs	Neutral/released	0
	Kicking about	1
	Tightened	2
Motor restlessness	None	0
	Moderate	1
	Restless	2

Table 2: Patient characteristics, type and duration of surgery

Variables	Group L	Group R
Age in years Mean±SD	4.23±1.3	4.47±1.46
Weight (in kilograms) Mean±SD	13.70±2.32	13.73±2.48
Sex ratio Male: Female	24:6	22:8
ASA physical status(I/II)	26/4	25/5
Type of surgery		
Inguinal hernia repair	27	28
Orchidopexy	3	2
Duration of surgery (in minutes) Mean±SD	51.5±5.59	49.83±5.65

SD = Standard Deviation

Group L= Levobupivacaine - Clonidine, Group R= Ropivacaine - Clonidine

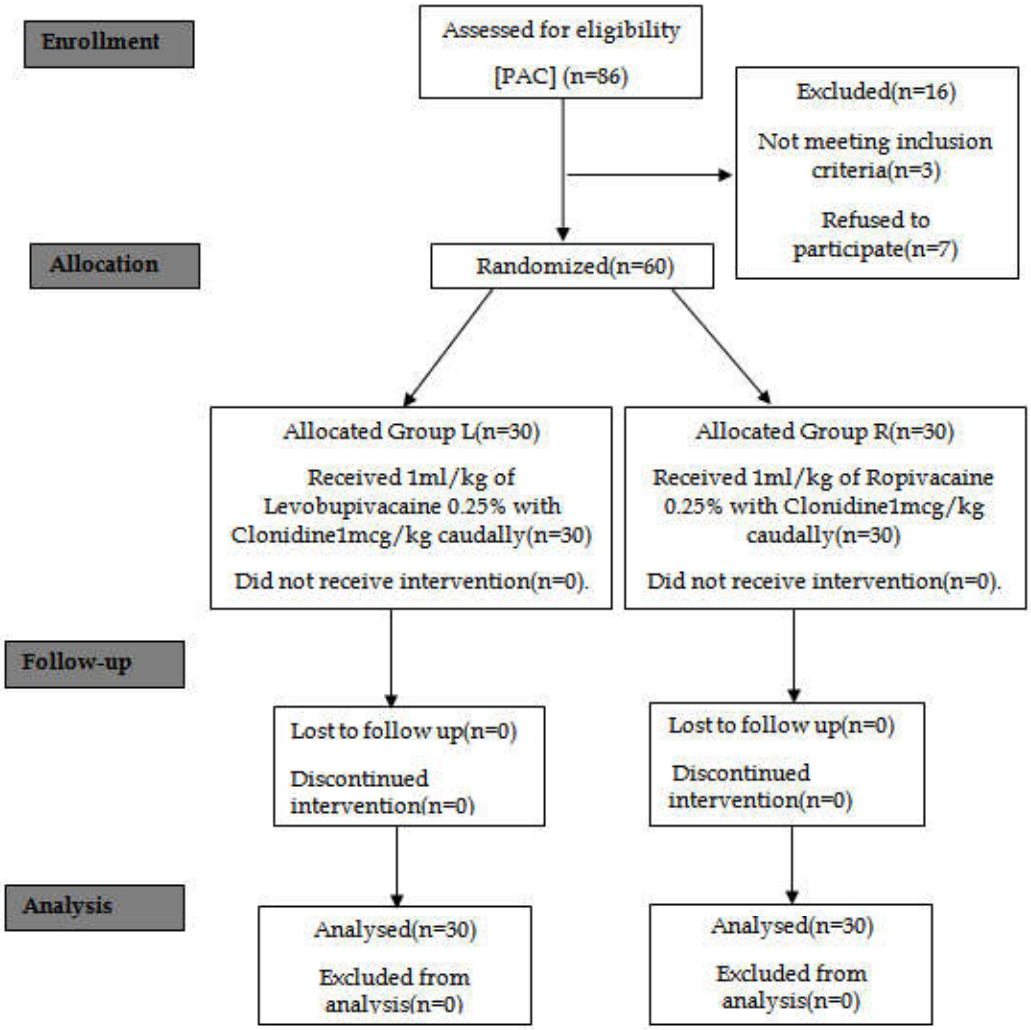


Fig. 1: Consolidated Standards of Reporting Trials flow diagram showing patient progress through the study phases

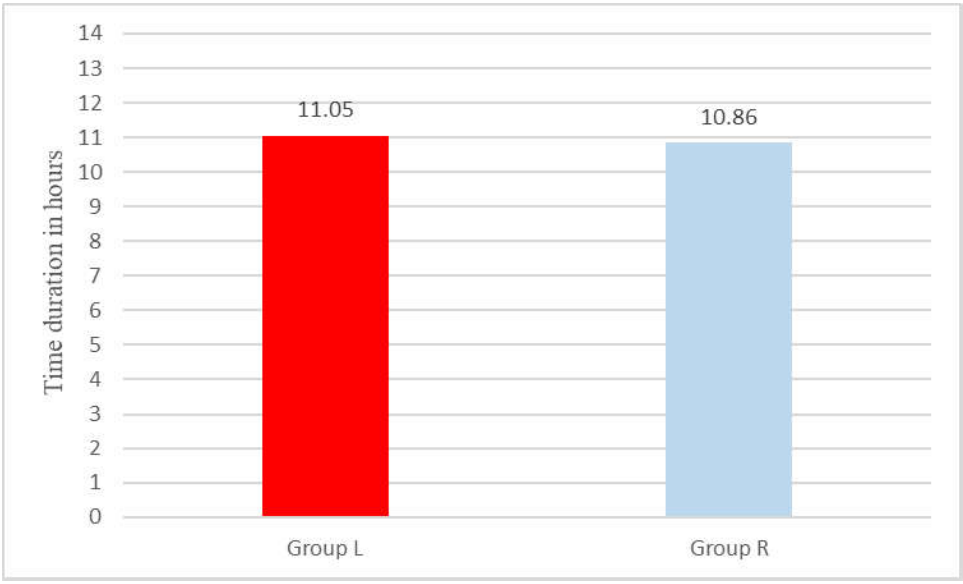


Fig. 2: Comparison of mean duration of analgesia (in hours)

Table 3: The comparison of sedation scores of patients in both the groups

UMSS score	Group L	Group R
0	8	10
1	20	18
2	2	2
3	0	0
4	0	0

UMSS=University of Michigan Sedation Scale

Group L= Levobupivacaine - Clonidine, Group R= Ropivacaine - Clonidine

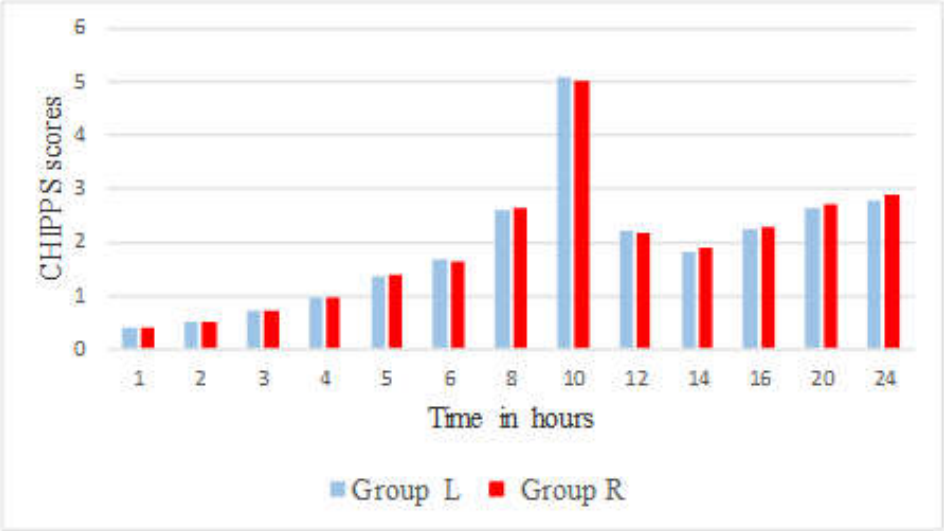


Fig. 3: The comparison of mean Children and Infants Postoperative Pain Scale (CHIPPS) scores in Group L and Group R.

Group L= Levobupivacaine - Clonidine, Group R= Ropivacaine – Clonidine.

Table 4: Duration of analgesia in the published literature

References	Authors	Surgery	Clonidine (mcg/kg)	Local anaesthetic agent	Duration of analgesia (in hours)	Pain Scale used
9	Kanaujia S K and colleagues	Lower abdominal surgeries	1 mcg/kg	Levobupivacaine 0.25% (1 ml/kg)	10.39±0.38	FLACC
16	Potti R L and colleagues	Hypospadiasis repair,inguinal herniotomy	1 mcg/kg	Levobupivacaine 0.25%(1 ml/kg)	16.68±4.7	CHIPPS
15	Manickam A and colleagues	Subumbilical and urological surgeries	1 mcg/kg	Ropivacaine 0.1% (1 ml/kg)	9.8	FLACC
2	Bajwa SJS and colleagues	Inguinal Hernia repair	2 mcg/kg	Ropivacaine 0.25% (0.5 ml/kg)	13.4±3.4	OPS

FLACC: Face, Legs, Activity, Cry, Consolability OPS: Objective Pain Score CHIPPS: Children and Infants Postoperative Pain Scale.

Results

Figure 1 shows the flow of patients through the trial. The groups were comparable with respect to age, weight, gender, ASA physical status, type of surgery and mean duration of surgery as conveyed by Table 2. All the caudal blocks were regarded successful as none required additional doses of intravenous fentanyl. Intraoperative haemodynamic parameters were within 20% of baseline value in both the groups.

The mean duration of analgesia (primary outcome) in group L was 11.05±0.26 and in group R was 10.86±0.22 hours respectively, implying no much difference in duration of analgesia (p value =0.84) between the groups [Fig. 2]. CHIPPS

score were comparable between the groups throughout the study period [Fig. 3]. Both the group required only one dose of rescue analgesic in the first 24 hours.

As evident from the Table 3, Sedation scores were lower as well as similar in both the groups and difference was not statistically significant. There were no complications in the 60 study patients, like nausea, vomiting, bradycardia, hypotension and respiratory depression in the post operative period.

Discussion

Ropivacaine and levobupivacaine are the newer local anaesthetic agents, which are associated with reduced systemic toxicity and hence has greater margin of safety [13]. Clonidine an alpha 2 adrenoreceptor antagonist is one of the widely used adjuvant in caudal block to prolong the duration of analgesia. Clonidine when given neuraxially, its analgesic effect was more pronounced, suggesting spinal mode of action. Sharp and colleagues, in their study found that, a lesser volume of bupivacaine (0.5 ml/kg) after caudal injection may not deliver the clonidine up to the spinal cord, there by leaving only direct action on nerve roots in the caudal area [19]. Further studies on ropivacaine showed that 1 ml/kg 0.25% ropivacaine when administered caudally, produces a maximal plasma concentration of 0.72±0.24 mg/lit(litre), which is way much lower than the maximal plasma concentration of ropivacaine (2.2±0.8 mg/lit) tolerated in adult volunteers [7]. Ingelmo P and colleagues in their study about relative analgesic potencies of levobupivacaine and ropivacaine for caudal anaesthesia in children found that the potency ratio at Effective Dose(ED)50 was 0.92 and at ED95 was 0.89, suggesting similar potency between the two anaesthestic agent in caudal block [8]. Therefore, we chose 1 ml/kg of 0.25% ropivacaine and levobupivacaine. Various doses of clonidine have been used caudally (1–5 mcg/kg), we selected a dose of 1 mcg/kg as it produces similar effect and fewer adverse effects when compared to 2 mcg/kg of clonidine [5].

In the present study, the primary outcome was the duration of analgesia (time duration from administration of caudal block to first requirement of rescue analgesia) which was comparable between the groups (around 11 hours). The duration of analgesia in other studies varied between 5.8 hours to 16.5 hours. This wide range of variation might be due to the difference in the dosage of clonidine, dosage and concentration of local anaesthetics agents, use of various premedication, different scales of pain assessment, indication for rescue analgesia and drugs used for rescue analgesia. Non standardised surgeries and anaesthetic techniques might be the other major factors. [1,2,9,15,16] [Table 4].

Sedation after clonidine is due to alpha 2 adrenoreceptor activation in locus ceruleus, an important modulator of vigilance, resulting in increased activity of inhibitory interneurons to produce central nervous system depression. It is dose-dependent as demonstrated by Lee and colleagues in their study on adding 2 mcg/kg of clonidine [12]. As we used lower dose of clonidine in our study, we had lower sedation scores in both the groups score and all the patients were easily arousable, which are consistent with the findings of previous studies [9,15,16]. Hypotension and bradycardia are the two haemodynamic side effects of clonidine in neuaxial blocks. This is due to stimulation of alpha 2 inhibitory neurons in the medullary vasomotor centre of the brainstem causing a decrease in sympathetic outflow. These are more pronounced in adults and with higher dose of clonidine. Because of lower dose of clonidine (1 mcg/kg) in our study, heart rate and mean arterial pressure were maintained within 20% of the baseline value and were comparable between the groups, which were similar to the previous study [29]. There have been documentation of respiratory depression with the use of caudal clonidine, which were more pronounced in neonates; 20 None of the patients in our study suffered this side effect [9,15,16]. A systematic review and meta-analysis by Yang Y and colleagues on Clonidine as additive to local anaesthetics for paediatric neuraxial blocks, demonstrated the increase in the duration of post operative analgesia, lesser number of rescue analgesic requirement and fewer side effects when lower doses were used. We found similar results in our study [20].

The standardised method of premedication, anaesthesia and analgesia are strengths of our study. Further we used CHIPPS score for pain assessment, which is a simple, objective and validated scale for assessing post-operative pain in children aged 1-6 years [3]. The pain was assessed for 24 hours postoperatively by anaesthesiologists and didn't involve parents. This was to prevent any bias or inconsistency in treating pain among kids. Ours was a single centric study with a small sample size. We didn't measure the motor blockage characteristics. We included children undergoing both inguinal hernia and orchidopexy, thus surgeries were non standardised. These were the limitations of our study.

Conclusion

Clonidine (1 mcg/kg) when added to levobupivacaine 0.25% and ropivacaine 0.25% in paediatric caudal block had similar post operative analgesia with fewer side effects and either combination can be used safely in children undergoing sub umbilical surgery.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Appendix

University of Michigan Sedation Scale (UMSS).

References

1. Akin A, Ocalan S, Esmaoglu A, Boyaci A. The effects of caudal or intravenous clonidine on postoperative analgesia produced by caudal levobupivacaine in children. Paediatr Anaesth. 2010;20(4):350-5.
2. Bajwa SJS, Kaur J, Bajwa SK, Bakshi G, Singh K, Panda A. Caudal ropivacaine- clonidine: A better post-operative analgesic approach. Indian J Anaesth 2010;54:226-30.
3. Buttner W, Finke W. Analysis of behavioural and physiological parameters for the assessment of postoperative analgesic demand in newborns, infants and young children: A comprehensive report on seven consecutive studies. Paediatr Anaesth. 2000;10:303-18.
4. Casati A, Baciarello M. Enantiomeric local anaesthetics. Can ropivacaine and levobupivacaine improve our practice? Curr Drug Ther. 2006;1:85-9.
5. Galante, D, Dambrosio M, Pellico, G, Federico A. A comparison of clonidine 1 mcg/kg vs clonidine 2 mcg/kg for caudal block with levobupivacaine 0.25% in paediatric patients .European Journal of Anaesthesiology. 2007;24:137.
6. Gunter JB. Benefit and risks of local anaesthetics in infants and children. Paediatr Drugs. 2002;4: 649-72.
7. Habre W, Bergesio R, Johnson C, Hackett P, Joyce D, Sims C. Pharmacokinetics of ropivacaine following caudal analgesia in children. Paediatric Anaesthesia 2000;10(2):143-7.
8. Ingelmo PM, Locatelli BG, Sonzogni V, Ggattoni C, Cadisco A, Lorini M, et al. Caudal 0.2% ropivacaine is less effective during surgery than 0.2% levobupivacaine and 0.2% bupivacaine: A double-blind, randomized, controlled trial. Paediatr anaesth. 2006;16:955-61.
9. Kanaujia SK, Singh PK, Kushwaha BB, Shyam R, Singh D, Chandra G et al. Comparative study of post-operative caudal analgesia for paediatric patients undergoing lower abdominal surgery. International Journal of Current Advanced Research 2016;5(6):1008-1011.
10. Krane EJ. Delayed Respiratory Depression in a Child after Caudal Epidural Morphine. Anesth Analg. 1988;67(1):79-81.
11. Laha A, Ghosh S, Das H. Comparison of caudal analgesia between ropivacaine and ropivacaine with clonidine in children: A randomized controlled trial. Saudi J Anaesth. 2012;6(3):197-200.
12. Lee JJ, Rubin AP. Comparison of bupivacaine clonidine mixture with plain bupivacaine for caudal analgesia in children. Br J Anaesth. 1994;72:258-62.
13. Locatelli B, Ingelmo P, Sonzogni V, Zanella A, Gatti V, Spotti a, *et al*. Randomized, Double blind, phase iii, controlled trial comparing Levobupivacaine 0.25%, ropivacaine 0.25% and Bupivacaine 0.25% by the caudal route in children. Br j anaesth. 2005; 94:366-71.
14. Malviya S, Voepel-Lewis T, Tait AR, Merkel S, Tremper K, Naughton N, et al. Depth of sedation in children undergoing computed tomography: Validity and reliability of the University of Michigan Sedation Scale (UMSS). Br J Anaesth. 2002;88:241-5.
15. Manikam A, Vakamudi M, Parameswari A, Chetan C. Efficacy of clonidine as an adjuvant to ropivacaine for caudal analgesia in children undergoing subumbilical surgery. J Anaesthesiol Clin Pharmacol. 2012;28(2):185-9.
16. Potti LR, Bevinaguddaiah Y, Archana S, Pujari VS, Abloodu CM. Caudal Levobupivacaine Supplemented with Caudal or Intravenous Clonidine in Children Undergoing Infraumbilical Surgery: A Randomized, Prospective Double-blind Study. Anesth Essays Res. 2017;11(1):211-5.
17. Rajagopal MR, Joranson DE. India: Opioid availability. An update. J Pain Symptom Manage. 2007;33:615-22.
18. Schnabel A, Poepping DM, Pogatzki Zahn EM, Zahn PK. Efficacy and safety of clonidine as additive for caudal regional anesthesia: A quantitative systematic review of randomized controlled trials. PediatrAnesth. 2011;21(12):1219-30.
19. Sharpe P, Klein JR, Thompson JP, Rushman SC, Sherwin J, Wandless JG. Analgesia for circumcision in a paediatric population: comparison of caudal bupivacaine alone with bupivacaine plus two doses of clonidine. Paediatr Anaesth. 2001;11:695-700.
20. Yang Y, Yu LY, Zhang WS. Clonidine versus other adjuncts added to local anesthetics for pediatric neuraxial blocks: A systematic review and meta-analysis. J Pain Res. 2018;11:1027-36.

Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(1) (Part - II): 235-240
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.33

Study on Oral Nebivolol in Attenuating the Cardio Vascular Responses to Laryngoscopy and Endotracheal Intubation

Anil Kumar Akkenapalli

Associate Professor, Department of Anesthesiology, Gandhi Medical College/ Gandhi hospital, Secunderabad, Telangana 500003, India.

Abstract

Introduction: Laryngoscopy and intubation are almost always associated with hemodynamic changes due to sympathetic discharge caused by epipharyngeal and laryngopharyngeal stimulation. *Aim:* To study the efficacy of oral Nebivolol in attenuating the cardio vascular reflex responses to laryngoscopy and endotracheal intubation. *Materials and methods:* The attenuation of cardiovascular reflex responses to laryngoscopy and endotracheal intubation has been done with oral nebivolol, a long acting beta-1 blocker in 25 healthy ASA grades 1 patients of both sexes b/w age groups 25-60 yrs. and compares with 25 others in the same age group, termed as control. The study group receives oral nebivolol 5 mg once daily for those below 50 kgs. In the premedication inj. Glycopyrolate 0.2 mg IM and inj. Ketorolac 1 mg/kg IM was given in both groups, inj. Glycopylate was preffered over injection atropine as it has better antisecretory properties with minimal cardiac effects, which would change basic monitoring values. *Results:* Laryngoscopy and endotracheal intubation there was significant increase in blood pressure (SAP, DAP and MPA) and heart rate in the control group, but was significantly less in the study who received the beta blocker nebivolol. In control group rate pressure product, a measure of myocardial oxygen demand was increased significant after laryngoscopy and endotracheal intubation. *Conclusion:* Hence, because of long duration of action and being beta, selective agent, oral nebivolol agent when used prior to surgery ensures a stable normotensive or a mild hypotensive field during surgery.

Keywords: Nebivolol; Laryngoscopy; Endotracheal Intubation.

How to cite this article:

Anil Kumar Akkenapalli. Study on Oral Nebivolol in Attenuating the Cardio Vascular Responses to Laryngoscopy and Endotracheal Intubation. Indian J Anesth Analg. 2019;6(1):235-40.

Introduction

Endotracheal intubation is translaryngeal placement of endotracheal tube into trachea via, the nose or mouth. It was during the world war-I that blind naos-tracheal intubation was popularized by rowbotham and Magill. Continued improvement in equipment and use of neuromuscular blockers combined with technical skills of anesthesiologist have made endotracheal intubation safe in common practice in modern day anesthesia. Commonly observed cardiovascular effects seen during intubation arehypertension and tachycardia which have been recognized since.

Direct recording of sympathetic nervous activity is difficult in man, but measurement of plasma

Corresponding Author: Anil Kumar Akkenapalli, Associate Professor, Department of Anesthesiology, Gandhi Medical College/ Gandhi hospital, Secunderabad, Telangana 500003, India.

E-mail: anilkumarakkenapalli@gmail.com

Received on 24.10.2018, **Accepted on** 03.10.2018

catecholamine has demonstrated increase in noradrenaline following laryngoscopy.

Attempts were made to differentiate between the effects of laryngoscopy and those of tracheal intubation and their individual contribution to hemodynamic changes. Prys Roberts et al. [1] observed that a majority of patients had reflex tachycardia and hypertension well before the act of intubation and this was often enhanced by intubation. So, it is laryngoscopy rather than endotracheal intubation, which generates the stimulus.Increase in heart rate and blood pressure is transitory, variable and unpredictable. the CVS response to intubation is exaggerated in hypertensive patients.

Cardiovascular response to intubation is of a serious concern in patients with hypertension, raised intracranial pressure, diseased cerebral vasculature or with ischemic heart disease where increase in myocardial oxygen consumption can lead to myocardial infraction [2,3]. Cardiovascular effects are observed during induction, during and after intubation during recovery of the patient. The various complications observed during endotracheal intubation are arrhythmias, myocardial ischemia, acute left ventricular failure, intracranial hemorrhage and pulmonary edema. Convulsions may be precipitated in eclamptic patients. Almost all types of dysrhythmias have been reported in addition to sinus tachycardia. The common abnormalities are nodal rhythm, atrial and ventricular extra systoles and pulses alternans. Less commonly, multifocal extrasystoles, pulsus bigeminus and atrial fibrillation have been reported. Heart block, ventricular tachycardia and fibrillation are fortunately rare. Radionuclide studies have shown that stress response to laryngoscopy and endotracheal intubation produce a rapid decline in global left ventricular function (ejection fraction) within seconds, often exercise in patients with symptomatic artery disease. Therefore, various techniques have been used to attenuate these responses. there are local, central and peripheral methods to achieve this purpose.Theseinclude topical and intravenous lignocaine, deep inhalational anesthetics, ganglion blockers, precurarization, narcotics (morphine, buprenorphine fentanyl, alfentanyl) adrenoceptor blocking drugs, vasodilators, nitroglycerin ointment, intranasal nitroglycerin, calcium channel blockers, reducing the duration of direct laryngoscopy to less than 15 seconds and avoiding laryngoscopy and resorting to blind nasal intubation.

Present study is undertaken to evaluate the efficacy of a new beta blocker viz., oral Nebivolol, a novel long acting beta blocker with endothelial protection activity, to attenuate cardiovascular Reponses to laryngoscopy and endotracheal intubation in health, ASA grade I normotensive patients.

Material and Methods

Fifty healthy ASA grades 1 patients scheduled for elective general surgery were selected forth present study Patients in group of 25 yrs. to 60 yrs. of either sex were selected and their weight, age and sex were comparable in both the groups. These fifty patients divided into two groups, control group consisting of 25 patients and study group consisting of 25 patients.

Complete paranesthesia checkup was done 3-4 days prior to surgery, detailed history taken and complete physical examination performed and presence of any organic medical disorder and history of other drug intake was excluded. Patients with history of angina, asthma, other respiratory disorders like COPD, atelectasis, pneumothorax, tuberculosis, haemothorax, pneumothorax were excluded from the study. patients with raised intracranial pressure were also excluded.

Patients with ECG changes of coronary artery disease, cardiac conducting defects, left ventricular hypertrophy, bradycardia (HR<60) congestive cardiac failure, cardiac valvular abnormalities myocardial disease another congenital cardiac defect were also excluded.

Laboratory Investigations: the laboratory investigation performed included a haemogram, serum creatinine, blood sugar, ECG and chest X-ray. Patients in study group were started 3-4 days prior to surgery with tab. nebivolol (nubeta) 5 mg/day orally for those weight was below fifty kilograms (50 kgs). Those patients, whose weight was greater than fifty kilograms (>50 kgs) were given tab nebivol (nublet) 10 mg/day. The drug was allowed to be taken at 8:00 AM every morning beginning 3-4 days prior to surgery. The last dose of nebivolol was given to the patients 4-6 hrs prior to induction of anesthesia with sip of water (upto ½ glass of water).

The drugs used to premedication and muscle relaxation to facilitate intubation were standardized for two groups (study and control). Boyled machine and circuits were thoroughly checked and required size endotracheal tubes and a Macintosh curved blade laryngoscope with required sized blades was kept. Before induction of anesthesia, patients

pulse rate, blood pressure and ECG monitoring started. This was done by monitoring with ECG in the standard limb leads along with SP02 maintaining. An adult sphynomanometer cuff tied to the left arm and attached to non-invasions blood pressure monitor.

Premedication: premedication was given with glycopyrrolate 0.2 mg and ketocele 1 mg/kg body weight intramuscularly 60 minutes before induction.

Induction: induction was done with thropentone sodium, dose of 5 mg/kg.

Intubation: intubation was performed with vecornium bromide with a dose of 0.1 mg/kg muscle relaxant used was vecuronium bromide for maintenance of anesthesia.

Patients requiring intubation time more than 40 seconds were excluded from the study. Halothane was used in maintenance of anesthesia only 15 minutes after induction prevent wrong interpretation. at the end of surgery, the residual neuromuscular was reversed with neostigmine 0.05 mg/kg and atropine 0.02 mg/kg.

Systolic blood pressure, diastolic blood pressure and heart rate were recorded at regular intervals in both control and study group as follows.

Just before induction, after induction at 1^{st}, 2^{nd}, 3^{rd}, 4^{th}, 5^{th}, 10^{th} and 15^{th} minutes.

Results

The characteristics of patients are shown in the following anthropometric

Table 1: Demographic details in both groups.

Demographic details	Control(n=25) Mean(SD)	Study(n=25) Mean(SD)
Age in Yrs	36.68(8.09)	40(10.35)
Range	28-44	30-40
Weight(kgs)	50.00(11.31)	51.56(5.59)
Range	43-60	40-58
Male/female(nos)	14/11	16/9
Range	26-56	25-60

There is no significant difference of demographic parameters in both groups.

Table 2: Hemodynamic reading recorded at the time of pre-anesthetic checkup.

Pre-anesthetic checkup	Control group n=25 Mean(SD)	Study group n=25 Mean(SD)	P-Value
SPD (mm Hg)	119.6(12.74)	127.44(15.88)	p>0.05
DAP (mm Hg)	76(7.64)	78.8(11.58)	p>0.05
MAP (mm hg)	99.23(6.31)	100.2(7.01)	p>0.05
heart rate (beat / minute)	88.32(9.86)	91.6(9.02)	p>0.05

Hemodynamic reading recorded at the time of pre-anesthetic checkup are shown above in the table are heart rate, systolic arterial pressure (SAP) diastolic arterial pressure (DAP) are almost similar in both control and study groups and there are no significant differences at the time of pre-anesthetic checkup.

In control group also standardized with same pre-medication the value taken as pre-induction values (basalvalues) in study and control group. Hemodynamic readings heart rate, systolic arterial pressure (sap), diastolic arterial pressure (DAP) are amount similar in both (control with study) group and there is insignificant difference at the time of pre-anesthetic checkup.

Following induction, there is fall in systolic, diastolic and mean arterial pressures in both groups compared to theirpre-inductionvalue (basal values) respectively the fall is significantly statistically in the same group and between the two groups ($p<0.05$). more significant in MAP and heart rate (HR). There is rise in the heart rate in both groups

Table 3: Hemodynamic values recorded at the time of induction (pre-induction)

Pre-induction	Control group n=25 Mean(SD)	Study group n=25 Mean(SD)	P-Value
SPD (mm Hg)	121.68(11.44)	113.2(16.66)	P<0.005 significant
DAP (mm Hg)	77.92(6.56)	70.2(11)	p>0.10
MAP (mm hg)	92.51(7.26)	85.2(8.86)	P<0.001 significant
heart rate (beat / minute)	91.28(9.79)	78.12(7.79)	P<0.001 significant
Rate pressure product (RPP)	11048.64	10900.40	p>0.10
After induction			
SAP (mm hg)	119.52(20.53)	101.16(14.40)	P<0.005 significant
DAP (mm hg)	79.72(8.6)	68.12(11.95)	P<0.05 significant
MAP (mm hg)	90.70(6.00)	80.00(9.40)	P<0.001 significant
Heart rate (beat/mt)	105.08(11.88)	86.96(8.62)	P<0.001 significant
Rate pressure product	12670.12	9267.60	P<0.001 significant

Table 4: Hemodynamic responses to laryngo scopy and endotracheal intubation

Cardio Vascular parameters	1 minutes after laryngoscopy and intubation	2 minutes after laryngoscopy	3 minutes after laryngoscopy	4 minutes after laryngoscopy	5 minutes after laryngoscopy	10 minutes after laryngoscopy	15 minutes after laryngoscopy
SAP in mmHgs	152.4 (12.34) 129.6 (15.67)	150.96 (13.57) 115.8 (15.52)	149.56 (13.25) 111.52 (14.93)	147.04 (15.13) 110 (16.33)	146.4 (15.53) 109.6 (16.20)	142.72 (10.70) 109.2 (14.70)	139.68 (19.34) 106.80 (14.06)
DAP in mmHgs	88.88 (7.21) 81.48 (9.67)	86.64 (7.20) 78.80 (9.19)	85.60 (7.37) 74.16 (10.13)	83.60 (7.37) 72.96 (10)	81.44 (7.06) 72.96 (10)	81.84 (6.40) 71.36 (7.83)	81.44 (6.15) 70.64 (8.85)
MAP in mmHgs	110.00 (7.05) 98.16 (8.90)	106.08 (8.62) 91.03 (6.92)	104.29 (6.97) 84.51 (8.35)	102.75 (5.80) 86.33 (8.92)	105.33 (8.67) 85.17 (5.08)	115.26 (10.40) 95.36 (6.82)	100.58 (12.23) 86.93 (7.96)
Heart rate beat/minutes	121.92 (6.28) 99.8 (5.92)	121.6 (5.26) 86.88 (5.39)	120.36 (4.54) 79.6 (8.30)	119.2 (5.42) 76.64 (5.71)	118.52 (4.20) 76.32 (5.82)	118.04 (4.42) 75.4 (4.55)	117.36 (4.35) 73.84 (4.2)
Rate pressure product	18492.00 11990.82	18356.73 11896.63	17920.64 887640	17467.67 8754.00	17128.00 8236.27	16893.67 8233.68	16382.84 7896.11

SAP- Systolic arterial pressure, DAP-Diastolic arterial pressure, MAP-Mean arterial pressure

HR- Heart rate, RPP=Rate pressure product

after induction this also significant ($p<0.001$) statistically.

In the control group the hemodynamic values increased very much above the basal values.

Systolic arterial pressure -30.72

Diastolic arterial pressure -10.96 mmHg

Mean arterial pressure -17.49 mmHg

Heart rate -30.64/beat/min

In the study group the difference is as follows:

Systolic arterial pressure -18.4 mmHg

Diastolic arterial pressure -9.28 mm Hg

Mean arterial pressure -12.96 mmHg

Heart rate -23.68 beats/minutes

This comparison gross increase in the hemodynamic responses to pre-induction readings (basal values) they are significant statistically.

Difference b/w the two groups (control and study) i.e., systolic arterial blood pressure ($p<0.001$), diastolic arterial pressure ($p<0.001$), mean arterial blood pressure ($p<0.001$) and heart rate ($p<0.001$) are statistically significant. There is also profound difference in rate pressure product values b/w control and study group.

There is not much difference b/w pre-induction value and 3 minutes after intubation. It shows attenuation response was achieved by 3rd minutes in study group, whereas in control group there is significant difference seen b/w pre-induction and there minutes and three after intubation values statistically.

The values 4 mints after intubation shows there is not much difference b/w control and study group compare three minutes after intubation values. Surgical incision was given five minutes after post intubation reading was recorded. All the patients were stable hemodynamically during the intra operative period and post-operative period; there was no incidence of bradycardia or hypertension during the study.

The values taken 10 min, 15 min, after intubation in respective tables both in control and study group without supplementing any drug. In control group the values did not touch the base line even by fifteenth minute after intubation. Whereas in study the values touched to base line by the 15th minute. This study shows nebivol was useful in attenuating the introduction response. At the end of surgery all the patients were reversed with neostigmine methyl sulphate and atropine sulphate. All the patients were followed in the post-operative period. There were no incidence of nauseas, vomiting, bradycardia, hypotension or any other untoward side effects.

Discussion

Reflex cardiovascular effects of laryngoscopy and endotracheal intubation in anaesthetized patients have been described previously and included a pressor response and tachycardia which occur at their peak approximately 30 minutes 45 seconds and the peak sustained till 1 minute after laryngoscopy and intubation [4].

There have been many studies which demonstrated increased sympathetic response to laryngoscopy and endotracheal intubations there changes during laryngoscopy and endotracheal intubation can lead to major complication like left ventricular failure, acute myocardial infarction, intracerebral hemorrhage In hypertensive patients this hyper dynamic response causes large increase

in myocardial oxygen demand Attempts to attenuate have responses by various drugs and techniques have met with varied success [5].

Various B. blockers have been used to attenuate the cardiovascular response to laryngoscopy and intubation with variable to reasonable amount of success [6]. In the present study oral nebovol a long acting beta-1 blockers (B1) 5 mg once daily started 3-4 days prior to surgery orally was usedto study its efficacy in the attenuation of pressor response to laryngoscopy and intubation. This study was conducted in normotensive, ASA grade -1 patents belonging to the age group 25-60 yrs, undergoing elective surgery.

The study consisted of 25 patients taken as control group and 25 patients taken as study group, who received tablet nebivolol 5 mg once orally and started 3-4 days prior to surgery. Both groups were pre-medicated with injection hetorlac 1 mg/kg weight I.M and glycopyrolate 0.2 mg IM 60-90 minutes before surgery. Blood pressure and heart rate response to laryngoscopy and intubation was studied in both groups who received the same drugs for induction and intubation. There was statistically no significant difference between the pre-inductionvalues of systolic diastolic arterial pressure sin both groups, but there is significant difference in mean arterial pressure and heart, rate statistically ($p<0.001$). mean arterial pressure, heart rate and rate pressure product ratios are lower in the study group who received tablet nebivolol.

After induction with thiopentone and vecuronium bromide difference in hemodynamic value b/w two groups was significant statistically in all the parameters, there was much fall in systolic arterial pressure and increase in heart rate to pre-induction values. One minute after laryngoscopy and intubation there was significant difference statistically in the hemodynamic values b/w the two groups ($p<0.001$). The increase in hemodynamic values till the 5th minute after intubation to pre-induction values in control group was significant statistically ($p<0.001$). so, this study confirms the potential hypertensive and tachycardia effects of laryngoscopy and intubation.

In the study group increase inhemodynamic values occurred till 2 minutes after intubation and almost touched the preinduction values (basal values) by 3rd minute change of hemodynamic values statistically only 1st one mte after intubation ($p<0.001$). In hemodynamic value the increase in study group compared to prelinduction values in two or 3 minutes intubation was not significant statistically. In the study group the difference observed at 3 minutes after laryngoscopy and endotracheal intubation to prenduction values as Heart rate 3.48 beats/minutes, Systolic arterial pressure as 0.32 mm Hg, Diastolic arterial pressure as 1.96 mm Hg, Mean arterial pressure as 69 mm Hg and Rate pressure product is also within the critical level (< 12,000). The changes in study group when compares to the changes in control group were statistically significant ($p<0.001$). this shows that oral nebivolol effectively attenuates the hemodynamic response to laryngoscopy and endotracheal intubation [7].

In the study groups the systolic, diastolic, mean arterial and heart rate have returned to the basal values, whereas in the control group the hemodynamic values are still above their basal values, whereas in the control group the hemodynamic values are still above their basal values and arte statistically significant ($p<0.001$) rate pressure product which denotes myocardial oxygen consumption was increased very much above the critical level 12,00 in the control groups after laryngoscopy and intubation but not in the study groups. The hemodynamic values in control group did not touch the basal values till 5 minutes after laryngoscopy and intubation the values are significant statistically ($p<0.001$). In the study group the hemodynamic values are similar to their values respectively which is not significant statistically at 5 mats after laryngoscopy and intubation.

There are not many studies on the effects of nebivolol a long acting B1 blocker on the attenuation of hemodynamic presser responses 6to laryngoscopy and intubation. Studies have been done on other B blockers i.e., atenolol, practolol, metoprolol, pindolol, esmolol, labettclol etc., The present study with nebivolol a new long acting beta blocker has given a positive result i.e., a good response of attenuation of hemodynamic responses to laryngoscopy and endotracheal intubation [8].

Study group patients were given Nebivolol (nubeta) orally 5 mg/day three (3) days before the surgery and on the day of surgery morning fourth day (4) at 5 AM with a sip of water and the patients were premediated with inj. Glycopyrrolate) 0.2 mg+inj. Ketorlac 1 mg/kg body weight IM and the hemodynamic value recorded. Significant changes of hemodynamic values were in study group.

Conclusion

The principal advantages observed with nebivolol during the study are Good attenuation of heart rate response, Good attenuation of blood response.

There was good intra operative protection against cardiovascular responses to surgical stimulation. There was good response to the pressor effects during extubating in most of the cases because of its long half-life. The during is easily available, easy to administer, cost is reasonable and needs to be administered only one a day. It has minimal side effects. No side effects were observed during the study.

It is concluded that enhanced sympathetic drive which results in hypertension and increased heart rate, associated with laryngoscopy and endotracheal intubation was attenuated with use of long acting beta-1 selective blocker tab. Nebivolol. The rate pressure product which is a major determinant of myocardial oxygen demand was also decreased because of the nebivolol.

References

1. Prys-Roberts C, Greene LT, Meloche R, Foëx P. Studies of anaesthesia in relation to hypertension. II. Haemodynamic consequences of induction and endotracheal intubation. Br J Anaesth. 1971;43:531–47.
2. Curran J, Crowley M, O′ Sullivan G. Droperidol and endotracheal intubation. Attenuation of pressor response to laryngoscopy and intubation. Anaesthesia. 1980;35:290–4. [PubMed].
3. Hamill JF, Bedford RF, Weaver DC, Colohan AR. Lidocaine before endotracheal intubation: Intravenous or laryngotracheal? Anesthesiology. 1981;55:578–81. [PubMed].
4. Henderson J. Airway management in the adult. In: Miller RD, editor. Miller's Anaesthesia. 7th ed. Philadelphia: Churchill Livingstone; 2010.pp.1573-1610.
5. Vermeulen TD et al. Influence of myocardial oxygen demand on the coronary vascular response to arterial blood gas changes in humans. Am J Physiol Heart Circ Physiol. 2018 Jul 1;315(1):H132-H140
6. Helfman SM, Gold MI, DeLisser EA, Herrington CA. Which drug prevents tachycardia and hypertension associated with tracheal intubation: lidocaine, fentanyl, or esmolol? Anesth Analg. 1991;72:482–6.
7. Ko SH, Kim DC, Han YJ, Song HS. Small-dose fentanyl: Optimal time of injection for blunting the circulatory responses to tracheal intubation. Anesth Analg. 1998;86:658–61.
8. Kautto UM. Attenuation of the circulatory response to laryngoscopy and intubation by fentanyl. Acta Anaesthesiol Scand. 1982;26:217–21.

Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; (Part - II) 6(1): 241-248
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.34

A Randomised Prospective Double Blinded Study of Intrathecal Levobupivacaine with Fentanyl Verses Clonidine for Infraumblical Surgeries

Greeshma N Murdeshwar[1], HG Manjunath[2], Somashekara SP[3]

[1]Assisstant Professor [2]Professor and Head [3]Post Graduate Student, Department of Anaesthesia, Mysore Medical College And Research Institute, Mysore, Karnataka 570001, India.

Abstract

Background and aims: Subarachnoid block can be performed with many local anaesthetic agents. Besides hyperbaric bupivacaine even isobaric levobupivacaine and ropivacaine can also be used with minimal cardiotoxicity. Adjuvants like opiods and alpha-2 agonist prolongs the duration of levobupivacaine action. The aim of the present study is to compare fentanyl and clonidine effect used as adjuvants to levobupivacaine with respect to onset of sensory and motor blockade; maximum level attained and the required for the same; duration of blockade and post operative analgesia. *Materials and Methods:* After ethical committee approval, 80 patients posted for infraumblical surgeries divided into two groups. Group LF received 15 mg of levobpivacaine with 25µg fentanyl whereas group LC received 15 mg of levobupivacaine with 30µg clonidine. The volume of solution was 3.5 ml in both groups. Hemodynamic, sensory and motor characteristics were monitored. *Results:* Onset of sensory and motor blockade as well as regression of both was faster with fentanyl than clonidine. There was slight fall in heart rate and mean arterial pressure in both the groups after intrathecal drugs but it was more with clonidine. Bradycardia and hypotension was noted more with clonidine than fentanyl which was easily manageable. Though the onset was delayed, sensory, motor and analgesic effect was prolonged with clonidine. *Conclusion*: Levobpiacaine can be safely used for spinal anaesthesia in infraumblical surgeries. Adding fentanyl causes early onset of action whereas clonidine has more prolonged action.

Keywords: Levobupivacaine; fentanyl; clonidine; spinal anaesthesia.

How to cite this article:

Greeshma N Murdeshwar, HG Manjunath, Somashekara SP. A Randomised Prospective Double Blinded Study of Intrathecal Levobupivacaine with Fentanyl Verses Clonidine for Infraumblical Surgeries. Indian J Anesth Analg. 2019;6(1):241-48.

Introduction

Spinal anaesthesia is the choice for infraumblical surgeries which includes lower abdominal, perineal and lower limb surgeries. It is a simple, cost effective technique having rapid onset of action with reliable sensory and motor blockade [1].

Levobupivacaine is a pure S-enantiomer of racemic bupivacaine (S-1nbutyl-2 piperidyl formo 2′6′ xylidide hydrochloride). It is a newer long acting local anaesthetic agent with minimal cardiovascular and central nervous system toxicity [2,3]. It is widely used in recent days for spinal anaesthesia and isobaric levobupivacaine alone has short lasting effect [4,5]. Addition of low dose adjuvants with local anaesthetic agents intrathecally improves the block quality and its duration [6]. The

Corresponding Author: HG Manjunath, Professor and Head, Department of Anaesthesia, Mysore Medical College and Research Institute, Mysore, Karnataka 570001, India.

E-mail: drhgmanjunathanes@gmail.com

Received on 16.11.2018, **Accepted on** 13.12.2018

adjuvants commonly used are opiods. Fentanyl has low risk of respiratory depression with rapid onset of action [7]. Intrathecal clonidine with alpha-2 agonistic activity is also an adjuvant potentiating the action of intrathecal drugs [8]. It reduces shivering and devoid of side effects associated with opiods like pruritis, nausea and vomiting, respiratory depression and urinary retention.

There are limited studies showing the difference in the effects of adjuvants like fentanyl verses clonidine with isobaric levobupivacaine for infraumblical surgeries. This triggered us to do the study to compare the potency of anaesthesia, hemodynamics and side effects between these two adjuvants in addition to isobaric levobupivacaine.

The primary objective of the study was to compare onset of sensory and motor blockade; maximum level attained and time required for the same; total duration of sensory and motor blockade and two segment sensory regressions time; postoperative analgesic requirement and hemodynamic effects. The secondary objective was to assess for any side effects like shivering, pruritus, nausea and vomiting, respiratory depression and sedation.

Materials and Methods

It is a prospective, randomised and double blinded study. After institutional ethical and scientific committee approval, 80 patients scheduled for the elective infra umbilical surgeries at our hospital were selected. Informed written consent was taken from the patients after the procedure was explained to them. Inclusion criteria were adult patients of either sex, aged between 18-55 years belonging to ASA class I or II with height between 154 to 174 centimetres. Exclusion criteria were patients belonging to ASA class III, IV, V and with Body Mass Index > 30 kg/m^2; or with absolute contraindications for spinal anaesthesia like raised intracranial pressure, severe hypovolumia, bleeding diathesis, local infection and history of allergy to any of the drugs.

The data were collected in a presetperforma meeting the objectives of this study. They were made aware of visual analogue score (VAS) scoring system required post operatively for pain assessment. They were randomly divided using sealed opaque envelope technique into 2 groups of 40 patients each. Group LF and Group LC. Group LF received 15 mg of 0.5% isobaric levobupivacaine with 25 µg of fentanyl whereas group LC received 15 mg of 0.5% isobaric levobupivacaine with 30 µg clonidine.

After preoperative assessment patients were kept fasting overnight. Patients were premedicated on the night before surgery with tablet ranitidine 150 mg and tablet alprazolam 0.5 mg. On morning of surgery intravenous (IV) line obtained with 18 guage cannula and preloaded with ringer lactate 10 ml/kg half an hour before anaesthesia. The monitoring was done using multiparameter monitor having pulse oximetry, electrocardiograph (ECG) and non invasive blood pressure (NIBP). Baseline pulse rate (PR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), electrocardiography (ECG) and arterial oxygen saturation (SpO_2) were noted. Patients were placed in lateral decubitus position with operative side downwards. Under aseptic precautions subarachnoid block was performed at level of L3-L4 through a midline approach using 25G Quincke's spinal needle. In both the groups the volume was kept constant up to 3.5ml by adding saline. Study drug was loaded by the senior anaesthesiologist who was not involved in the study. All spinal blockades was performed by the another anaesthesiologist, who was also the observer. Thus both patient and observer were blinded for the study. During injection operating table was kept flat. Patient was turned to supine posture immediately. Sensory blockade was tested using pinprick method with a blunt tipped 27G hypodermic needle at midclavicular line every 30 seconds for first 2 minutes, every minute for next 5 minutes and every 5 minutes for next 15 minutes and every 10 minutes for next 30 minutes and every 15 minutes till the end of surgery and there after every 30 minutes until sensory block is resolved. Quality of motor blockade was assessed by modified Bromage scale (MBS): 0 – patient is able to move the hip, knee and ankle; 1- patient is unable to move the hip but is able to move the knee and ankle; 2 – patient is unable to move the hip and knee but is able to move the ankle; 3- patient is unable to move the hip, knee and ankle and 4- patient is unable to move toes.

The following time were noted from the point of drug injection:

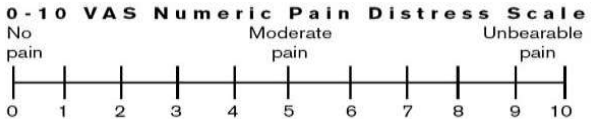
1. Onset of sensory blockade when the sensory loss was up to the T8 dermatome. Surgery was allowed to start when this level was attained. Onset of motor blockade which was the time taken for MBS to be one.
2. Maximum level of sensory and motor blockade attained and time taken for it.
3. Duration of sensory blockade which was time taken for sensory regression to L1 and

duration of motor blockade which was the time taken for MBS to be 1.

4. Two segments sensory regression time which is the duration between highest sensory level attained to two segment regression.
5. Total duration of analgesia was upto the period where patient had VAS of 4. Haemodynamics were monitored via PR, SBP, DBP, MAP, ECG and oxygenation monitored via SpO_2. If MAP decreases more than 30% of basal it was considered hypotension managed with IV ephedrine 6 mg bolus doseand fluid bolus at the rate of 2-3 ml/kg/hour. Heart rate decreasing to less than 50 was considered as bradycardia and it was treated with IV atropine 0.6 mg. If patient complained of pain regional was converted to general anaesthesia and they were excluded from the study. Total duration of surgery and side effects like nausea and vomiting, shivering, pruritus were also noted. Sedation was assessed using Ramsay's sedation score (RSS) every half an hourly after spinal anaesthesia. RSS is as follows: 1) anxious, agitated or restless; 2) co-operative, oriented and tranquil; 3) responds to commands; 4) asleep but has a brisk response to light glabellar tap or loud auditory stimulus; 5) asleep but has a sluggish response to light glabellar tap or loud auditory stimulus; 6) asleep no response.

Post operatively patient shifted to post anaesthesia care unit (PACU). Here hemodynamic, sensory and motor level and pain assessment via VAS (0-10) was done. Rescue analgesic IV diclofenac 75 mg was given if VAS score was 4 or above.

Statistical analysis was done using SPSS 19 version. Data are presented as mean and standard deviation. p value of < 0.05 was considered as significant and < 0.001 highly significant. Paired and unpaired t-test and analysis of variance was used for statistical calculations. Numerical variables were compared using chi-square test for nonparametric data and Student-t test for parametric data.



Results

Both LF and LC groups were comparable with respect to their demographic characteristics; duration of surgery and mean of baseline HR and BP as shown in Table 1 and type of surgeries as shown in Table 2.

Sensory onset time was significantly faster with fentanyl than clonidine. Average maximum sensory level attained in both the groups was 6.3 in group LF and 5.35 in group LC. Time to attend this level was statistically significantly shorter with fentanyl than clonidine. TSSR and SRL1 were also statistically significantly faster with fentanyl. This means the regression of spinal effect with fentanyl as additive was faster than clonidine as additive. Onset of motor blockade and time

Table 1: Demographic; surgical characteristics and mean of baseline heart rate and mean arterial pressure

Sl. No	Characters	Group LF	Group LC	p Value
1.	Age	37.37±10.65	36.15±10.8	0.611
2.	Sex (M:f)	31:9 (77.5% : 22.5%)	34:6 (85% :15%)	0.390
3.	American Society of Anesthesia Grade (I:ii)	22:18 (55% : 45%)	25:15 (62.5% : 37.5%)	0.496
4.	Body Mass I Ndex	22.66±1.53	22.91±1.22	0,423
5.	Duration of Surgery (Min)	134.37±33.28	126.05±28.88	0.236
6.	Mean Baseline Heart Rate	75.67±12.71	78.72±10.51	0.2
7.	Mean Baseline Of Mean Arterial Pressure	100.58±10.02	99.15±8.66	0.5

Table 2: Type of surgeries

Sl. No	Type of Surgeries	Group LF	Group LC	p Value
1.	Lower Abdomen	13	15	0.639
2.	Orthopedic Surgery	17	14	0.491
3.	Genital Surgeries	7	6	0.761
4.	Varicose Veins	3	5	0.711

Table 3: Sensory and motor characteristics in both the groups.

Sl. No	Characters	Group LF	Group LC	P Value
1.	Time of onset of sensory blockade -TOSB in seconds (minutes)	155.62 ±18.26 (2.59 min)	184.75±21.89 (3.07 min)	<0.005
2.	Maximum level of sensory blockade – MLSB	6.3±1.62	5.35±1.51	0.1662
3.	Time taken for maximum level of sensory blockade - TMLSB(min)	4.73±1.09	6.96±1.15	<0.005
4.	Two segment sensory regression-TSSR(min)	94.75±11.23	107.00±11.39	<0.005
5.	Sensory regression to L1-SRL1(min)	303.25±31.91	324.12±25.84	0.002
6.	Time of onset of motor blockade-TOMB(seconds)	198.62±23.12 (3.31 min)	245.00±36.37 (4.08)	<0.005
7.	Maximum level of motor blockade –MLMB	3.17	3.25	0.598
8.	Time taken for maximum level of motor blockade -TMLMB(min)	6.66±1.21	7.62±1.43	0.0354
9.	Total duration of motor blockade - TDMB(min)	287.12±20.7	298.25±21.03	<0.005

Table 4: Complications and postoperative analgesia in both groups.

Sl. No	Complications	Group LF	Group LC	P- Value
1.	Bradycardia	2 (5%)	5 (12.5%)	0.235
2.	Hypotension	3 (7.5%)	5 (12.5%)	0.456
3.	Nausea	1 (2.5%)	0	0.314
4.	Vomiting	2 (5%)	0	0.152
5.	Pruritis	3 (7.5%)	0	0.077
6.	Shivering	0	0	-
7.	No of Patients with Ramsay Sedation Score >2 at 90 Minutes	2 (5%)	8 (20%)	<0.005
8.	Postoperative Analgesia Duration (Minutes)	318.00±78.21	393.37±81.91	<0.005

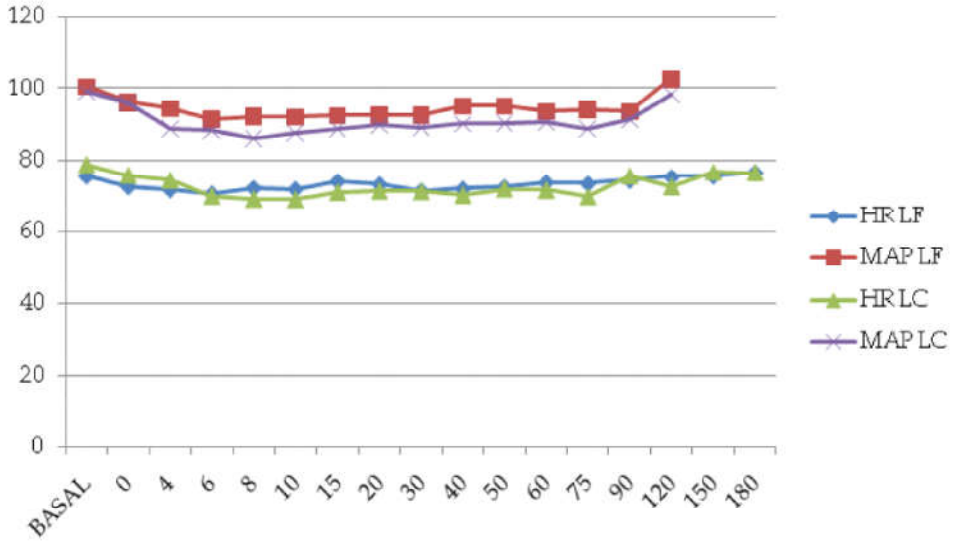


Fig. 1: Variation in HR and MAP after intrathecal block in both the groups.

taken for maximum motor blockade were earlier with fentanyl than clonidine. Average maximum motor blockade was around B3 in both the groups. Duration of motor blockade was lower in both the groups than sensory blockade (which is SRL1) but it was prolonged with clonidine than fentanyl as shown in Table 3.

There was fall in HR and MAP in both the groups after spinal anaesthesia. But there was statistically significant fall in HR and MAP with LC group than LF group during the first 15-30 minutes which was eventually managed as shown in figure-1. Bradycardia and hypotension was more with clonidine than fentanyl. One patient had nausea, two patients had vomiting and three patients had pruritus with fentanyl. Patients in clonidine group were more sedated than fentanyl after about 90 minutes after intrathecal drug injection administration.

Postoperative analgesia was statistically significantly longer with clonidine than fentanyl as shown in Table 4.

Discussion

There are many adjuvants available along with levobupivacaine agents to increase its potency. Fentanyl used in our study facilitates the afferent sensory blockade by stimulating μ1 and μ2 receptors in the spinal cord [9]. On the other hand clonidine prolongs the blockade by activation of post-synaptic α2 receptor in substantia gelatinosa of spinal cord [10].

In Glaser et al. study, who compared isobaric levobpivacaine 3.5 ml with isobaric bupivacaine 3.5 ml in hip replacement surgeries, onset of sensory blockade, was 11±6 minutes [11]. Compared to this the onset time of sensory blockade was shorter in our study. Though the volume of the intrathecal drug was similar as in our study, the adjuvants we used caused the shorter onset time of sensory blockade in our study. In Agarwal A P et al. sensory onset time was 2.62±0.95 minutes and motor onset time was 3.53±0.17 with intrathecal 3 ml levobupivacaine and 25 μg fentanyl in lower abdomen and lower limb surgeries [12]. In Bhavani V et al. sensory onset time was 6.03±1.923 minutes and motor onset time was 7.48±2.2 minutes with intrathecal 3 ml levobupivacaine and 30 μg clonidine in vaginal hysterectomy patients [13]. In our study sensory onset time was 155.62 seconds (2.59 minutes) and the motor onset time was 198.62 seconds (3.31 minutes) with isobaric levobupivacaine 3.5 ml combined with 25 μg fentanyl whereas sensory onset time was 184.75 seconds (3.07 minutes) and the motor onset time was 245.00 seconds (4.08 minutes)with isobaric levobupivacaine 3.5 ml combined with 30 μg clonidine in our study The dosage of intrathecal drug used in Agarwal AP et al. and Bhavani V et al. study were similar to our study and the sensory onset and motor onset time in both these studies are consistent to our study. In our study sensory onset and motor onset were statistically significantly faster with the adjuvant fentanyl than clonidine.

Glaser et al. also had highest sensory level at T8 level [11]. In our study the maximum sensory level attained with isobaric levobupivacaine was at an average of 6.3 when combined with fentanyl and 5.35 when combined with clonidine. In Filiz Karaca et al. and Nesrin Bozdogan et al. study the effect of isobaric levobupivacaine with fentanyl was observed in patients undergoing caesarean section [14,15]. Both the studies had highest sensory level of T4 level with levobupivacaine. The gravid uterus and raised abdominal pressure might have caused higher sensory level in the above studies. Camorcia M et al. who compared relative potencies for motor block after intrathecal ropivacaine, levobupivacaine, and bupivacaine reported intermediate motor blocking effects of levobupivacaine in his study [16]. In our study the average maximum motor block was MBS-B3 which correlates with the above study asthe complete motor blockade of MBS-B4 was hardly achieved with either of the group which signifies that adjuvant might have no much effect on levobupivacaine to enhance the motor blockade.

Agarwal archana et al. compared the effect of intrathecal fentanyl 15 μg with clonidine 30 μg on 2.5 ml of 0.5% isobaric levobupivacaine in the patients undergoing lower limb surgery [17]. Time to attend the peak sensory effect was 9.67±1.18 minutes with fentanyl and it was 9.70±1.32 minutes with clonidine. Though not statistically significant it was relatively lower with fentanyl. In our study, the time to attend maximum sensory blockade was 4.73 minutes with fentanyl and 6.96 minutes with clonidine. It was statistically significantly lower with fentanyl might be because of higher dose of fentanyl of 25 μg which we used. The delayed onset of maximum sensory effect with clonidine than fentanyl is also consistent with other studies where these two adjuvants were compared with different local anaesthetic agents like: Chabbra Anita R et al. assessed the effect of 60 μg clonidine verses 25 μg fentanylcombined with intrathecal 3 ml of isobaric 0.5% ropivacaine in lower limb surgeries. Here time to attend peak sensory level

was 6.86±3.73 minutes with fentanyl and 8.61±7.18 minutes with clonidine [18]. Sharan Radhe et al. compared the effect of 30 μg of clonidine verses 25 μg of fentanyl with 2.5 ml of 0.75% ropivacaine in lower abdomen surgeries. Here time to attend peak sensory level was 9.64±1.67 minutes with fentanyl and 9.68±1.78 minutes with clonidine [19]. Bajwa et al. compared 50 μg clonidine verses 25 μg fentanyl with 2.5 ml 0.5% hyperbaric bupivacaine in lower abdomen surgeries. Time for peak sensory onset was 7.34±0.96 minutes with fentanyl and 7.56±1.78 with clonidine [6]. The alteration in the values is because of different doses of adjuvants and the difference in local anaesthetic agents used.

In Nesrin Bozdogan et al. study where isobaric levobupivacaine was given with fentanyl the TSSR was 96.48±24.46 minutes and in Kuikarni J et al. study with isobaric levobupivacaine combined with clonidine the TSSR was 157.83±3.49 minutes [15,20]. Both the above mentioned study were done on patients undergoing lower segment caesarean section. This shows the faster regression action of fentanyl than clonidine. The observation in these two studies is in accordance to our study where we noticed TSSR of 94.75±11.23 minutes in fentanyl whereas it was 107.00±11.39 minutes with clonidine as additive to isobaric levobupivacaine. The difference was highly significant statistically.

In our study total duration of sensory blockade was 303.25±31.91 minutes and motor blockade was 287.12±20.7 minutes in fentanyl group. Total duration of sensory blockade was 324.12±25.84 minutes and motor blockade was 298.25±21.03 minutes in clonidine group. In Agarwal et al. study total duration of sensory blockade was 241.57±1.87 minutes and motor blockade was 187.48±12.12 minutes with 15 mg isobaric levobupivacaine and 25 μg fentanyl [12]. In Bhavani V et al. study total duration of sensory blockade was 288.87±18.651 minutes and motor blockade was 190.97±17.38 minutes with 15 mg isobaric levobupivacaine and 30 μg clonidine [13]. This is in accordance to our study as the drug volume and quantity in the above two studies is resembling our study. This suggests that clonidine has longer sensory and motor blockade effect compared to fentanyl as an adjuvant to isobaric levobupivacaine.

Duration of postoperative analgesia was 249.59±10.40 minutes in Agarwal A P et al. study and 288±18.6 minutes in Bhavani V et al. study with fentanyl and clonidine respectively [12,13]. Clonidine have more tendency to prolong the analgesia. This is also in accordance with Singh Baljit Bajwa et al. and Chabbra Anita et al. study who used both these adjuvants with bupivacaine and ropivacaine respectively [6,18]. Even in Agarwal Archana et al. study where both these adjuvants were used with isobaric levobupivacaine there was prolonged postoperative analgesia with clonidine than fentanyl in lower limb surgeries. Likewise in our study postoperative analgesia duration was highly statistically significantly prolonged with clonidine. It was 318.00±78.21 minutes with fentanyl and 393.37±81.91 minutes with clonidine as adjuvant to isobaric levobupivacaine. From the above mentioned studies it can be derived that clonidine hashigher potency than fentanyl to prolong the analgesic duration.

There was fall in BP in both the groups; more in the group LC from baseline immediately after intrathecal drug administration. This is similar to Glaser et al. study, which used volume of 3.5 ml of levobupivacaine for hip surgeries [11]. Around 5% patients in group LF and 12.5% patients in group LC had hypotension and around 7.5% of patients in group LF and 12.5% of patients in group LC bradycardia which was managed. Though not statistically significant these haemodynamic changes were, more with clonidine may be because of presynaptic noradrenaline inhibition and its action on atrioventricular node after systemic absorption [21].

Patra et al. reported 46% of patients had pruritus with fentanyl [22]. Similarly other investigators have also reported pruritis with fentanyl. Erkan et al. reported pruritus in around 25% of transurethral resection of prostate patients anaesthesised with intrathecal levobupivacaine and clonidine [23]. Liu S et al. also noticed pruritus with intrathecal fentanyl in his study [24]. In our study 5% of patients developed pruritus. The effect of pruritus was transient and hardly needed treatment. In our study 20% of patients had sedation with clonidine and 5% of patients in fentanyl. None had respiratory depression or fall in saturation. This is due to the action at nucleus cerueleus where hyperpolarisation of excitatory neurons takes place [25]. In Kothari et al. study, where 45 μg clonidine was added to bupivacaine in ceasserean patients there was sedation in 35% to 45% patients [26]. One patient in the fentanyl group had nausea and two patients had vomiting. Incidence of nausea and vomiting were noticed with intrathecal fentanyl in the literature [27].

Conclusion

There are many studies stating that levobupivacaine can be safely used for spinal

anaesthesia in infraumblical surgeries. With the adjuvants adequate level can be attained for lower abdomen and lower limb surgeries. Adding 25 µg fentanyl causes early onset of action whereas 30 µg clonidine to 15 mg isobaric levobupivacaine has more prolonged action. But isobaric levobupivacaine with clonidine is better than levobupivacaine with fentanyl because with clonidine there is longer duration of sensory blockade and postoperative analgesia. But there were more chances of hypotension and bradycardia with clonidine than fentanyl as well as prolonged effect can delay ambulation which can be easily managed. The hemodynamic parameters should be vigilantly monitored with these adjuvants and should be more meticulous when clonidine used.

References

1. Covino BG. Rationale for spinal anesthesia. International Anaesthesiology Clinics. 1989;27:8-12.
2. Bardsley H, Gristwood R, Baker H, et al. A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. Br J Clin Pharmacol. 1998;46:245–9.
3. Huang YF, Pryor ME, Mather LE, et al. Cardiovascular and central nervous system effects of intravenous levobupivacaine and bupivacaine in sheep. AnesthAnalg. 1998;86:797–804.
4. Girgin NK, Gurbet A, Turker G, Bulut T, Demir S, Kilic N, et al. The combination of low-dose levobupivacaine and fentanyl for spinal anaesthesia in ambulatory inguinal herniorrhaphy. J Int Med Res. 2008;36:1287–92.
5. Akan B, Yagan O, Bilal B, Erdem D, Gogus N. Comparison of levobupivacaine alone and in combination with fentanyl and sufentanil in patients undergoing transurethral resection of the prostate. J Res Med Sci. 2013;18:378–82.
6. Bajwa Baljit Singh, Singh Arwinder Pal and Rekhi. Comparison of intrathecal clonidine and fentanyl in hyperbaric bupivacaine for spinal anesthesia and postoperative analgesia in patients undergoing lower abdominal surgeries. Saudi J Anaesth. 2017 Jan-Mar;11(1):37–40.
7. Selvaraju KN, Sharma SV. Comparison of forced expiratory spirometric flow changes following intrathecal bupivacaine and bupivacaine with fentanyl. South Afr J AnesthAnalg. 2008;14:33–7.
8. Bonnet F, Buisson VB, Francois Y, Catoire P, Saada M. Effects of oral and subarachnoid clonidine on spinal anesthesia with bupivacaine. Reg Anesth. 1990;15:211–4.
9. Goel S, Bhardwaj N, Grover VK. Intrathecal fentanyl added to intrathecal bupivacaine for day case surgery: A randomized study. Eur J Anaesthesiol. 2003;20:294–7.
10. Shah BB, Joshi SS, Shidhaye RV, Lakhe JN. Comparison of different doses of Clonidine as an adjuvant to intrathecal Bupivacaine for spinal anesthesia and postoperative analgesia in patients undergoing caesarean section. Anaesth Pain and Intensive Care. 2012;16(3):266-272.
11. Christian Glaser, Peter Marhofer, Gabriela Zimpfer, Marie T. Heinz, Christian Sitzwohl, Stephan Kapral, and Ingrid Schindler. Levobupivacaine Versus Racemic Bupivacaine for Spinal AnesthesiaAnesthAnalg. 2002;94:194–8.
12. Agarwal A.P, Khan Mehvish, Agarwal Malti, Singh Rampal, Gopal Krishnan, Mitra Subhro. A comparision of intrathecal isobaric 0.5% levobupivacaine with fentanyl and isobaric 0.5% ropivacaine with fentanyl for lower abdomen and lower limb surgeries. A prospective randomized double blind controlled study. Annals of international medical and dental research. 2018;4(3):1-5.
13. Bhavani V, I Joseph Raajesh. Comparison of intrathecal isobaric levobupivacaine, levobupivacaine- clonidine, with hyperbaric bupivacaine as a control for quality of anaesthesia intraoperative hemodynamics and duration of post-operative pain relief in patients undergoing vaginal hysterectomy Indian Journal of Clinical Anaesthesia, 2016;3(2):148-54.
14. Filiz Karaca, Ezgi Erkılıç, Alev Akdıkan, Tülin Gümüş, Orhan Kanbak. Assessment of the effect of Intrathecal low dose levobupivacaine or bupivacaine combined with fentanyl in patients undergoing cesarean section. Journal of anesthesia & clinical research 2014;5(11):1-5.
15. Nesrin Bozdogan Ozyilkan, Aysu Kocum, Mesut Sener, Esra Caliskan, Ebru Tarim, Pinar Ergenoglu, Anis Aribogan. Comparision of intrathecal levobupivacaine combined with sufentanil, fentanyl or placebo for elective caesarean section: A prospective randomized double blind controlled study. Current therapeutic research. 2013;75:64-70.
16. Camorcia M, Capogna G, Berrita C, Columb MO. The relative potencies for motor block after intrathecal ropivacaine, levobupivacaine, and bupivacaine. AnaesthAnalg. 2007;104(4):904–7.
17. Agarwa Archana, Lakhotia Rajiv, Longwani Somnath, Srivastava Sandeep, Kumar Srivastava Amit and Bogra Jaishri. A comparison of fentanyl and clonidine as adjuvants to intrathecal levobupivacaine for spinal anaesthesia and postoperative analgesia in patients undergoing for lower limb surgery. International Journal of Biomedical Research. 2018;09(02):76-80.
18. Chabbra Anita R, Jagtap Sheetal R, Dawoodi Sunny F. Comparison of clonidine versus fentanyl as an adjuvant to intrathecal ropivacaine for major

lower limb surgeries: A randomized double-blind prospective stud. 2013;27(3):170-174.

19. Sharan Radhe, Verma Rajan, Dhawan Akshay, and Kumar Jugal. Comparison of clonidine and fentanyl as adjuvant to ropivacaine in spinal anesthesia in lower abdominal surgeries. Anesth Essays Res. 2016 Sep-Dec;10(3):526–31.
20. Kulkarni Jyoti, Lodha Veena, Patil Tushar and Misal Ullhas Comparison of Levobupivacaine and Clonidine with Bupivacaine and Clonidine in Spinal Anaesthesia for Lower Segment Caesarean. Journal of Dental and Medical Science. 2016 August;15(8): 92-97.
21. Anatassiou E, Karmiri E, Kolotoura A, Apostolaki S, Andreotti V, Chapsa Ch. Low dose intrathecal clonidine to levobupivacaine spinal anaesthesia for total knee arthroplasty. Regional anaesthesia and pain medicine 2003.
22. Patra P, Kapoor MC, Nair TG. Spinal anesthesia with low dose bupivacaine and fentanyl for endoscopic urological surgeries. J Anaesthesiol Clin Pharmacol 2005;21:147-54.
23. Erkan Yavuz Akcaboy, Zeynep Nur Akcaboy,and Nermin Gogus. Low dose levobupivacaine 0.5% with fentanyl in spinal anaesthesia for transurethral resection of prostate surgery J Res Med Sci. 2011 Jan;16(1):68–73.
24. Liu S, Chiu AA, Carpenter RL, Mulroy MF, Allen HW, Neal JM, et al. Fentanyl prolongs lidocaine spinal anaesthesia without prolonging recovery. AnesthAnalg. 1995;80(4):730–4.
25. Chandra Richa, Nanda Harjeet singh, Kumar Abhishek. Comparison of intrathecal Levobupivacaine versus Bupivacaine with Clonidine as adjuvant. International Journal of scientific study. 2014 Oct;2:(7).
26. Kothari N, Bogra J, Chaudhary AK. Evaluation of analgesic effects of intrathecal clonidine along with bupivacaine in cesarean section. Saudi J Anaesth. 2011;5:31–5.
27. Alain Borgeat, Georgios Kkatodramis, Carlo A Schenker. Post operative nausea and vomiting in regional anaethesia: a review. Anaesthesiology. 2003;98:530-47.

Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(1) (Part - II): 249-254
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.35

Comparison of Equipotent Doses of Hyperbaric Ropivacaine and Hyperbaric Levobupivacaine in Spinal Anaesthesia for Patients Undergoing Lower Abdominal and Lower Limb Surgeries

Gurpreet Singh[1], Niraj Mansukhlal Rathod[2], Kirti Patel[3]

[1]3rd Year Resident [2]Assistant Professor [3]Professor, Department of Anesthesia, SBKS Medical Institute and Research Centre, Pipariya, Vaghodiya, Vadodara, Gujarat 391760, India.

Abstract

Background: Spinal anaesthesia provides sensory as well as motor blockade. Levobupivacaine is less cardio toxic than bupivacaine, as it has decreased potency at the sodium channel. Ropivacaine is similar in chemical structure to bupivacaine, but it is less potent than bupivacaine. Intrathecal Ropivacaine is safe, has shorter duration of action than bupivacaine and lesser incidence of neurological symptoms as compared with intrathecal lignocaine. Literature suggest that potency of Ropivacaine is less when compared with levobupivacaine since it has lower lipid solubility, and thereby using an equipotency ratio of 1.5:1 between Ropivacaine and Levobupivacaine provides nearly similar efficacy outcome. *Method*: The study was carried out as prospective, interventional, double blind in 60 patients divided in two equal groups using equipotent doses of intrathecal hyperbaric Ropivacaine and hyperbaric Levobupivacaine (with ASA grading I and II). *Results:* The distribution of patients with respect to age, height, weight was statistically not significant in both the groups. (p value > 0.05). Mean time to onset of motor block was 25.07±1.97 minutes in group-L and 24.37±1.70 minutes in group-R. Average duration of motor block was 116.73±29.95 minutes in group-L and 112.93±15.40 minutes in group-R. Mean time to onset of sensory block was 17.07±1.93 minutes in group-L and 15.5 ± 1.81 minutes in group-R. Mean time to attain highest level of sensory block was 22.07±1.93 minutes in group-L and 20.5±1.81 minutes in group-R. Mean time to two segment regression of sensory block was 69±8.5 minutes in group-L and 61.83±6.31 minutes in group-R. Average duration of sensory block was 188.73±29.94 minutes in group-L and 192.2±36.01 minutes in group-R. There were no changes in vital parameters and oxygen saturation in the intra-operative and post-operative period. Mean duration of post-operative analgesia was 137.70±28.01 minutes in Group L and 131.2±38.97 minutes in Group R. Analgesic consumption for 24 hours postoperatively was similar in both the groups. It was observed that both the molecules showed similar time of onset of motor and sensory block and also nearly similar duration of motor and sensory blocks. Both the drugs were also found to be safe in terms of impact on hemodynamic parameters and no complications observed. *Conclusion:* Both drugs are reliable in terms of efficacy and safety and can be used interchangeably. Ropivacaine can be specifically used for population that is at higher risk of cardiac toxicity, without compromising on time of onset or duration of motor and sensory blocks.

Keywords: Spinal Anesthesia; pain; Ropivacaine; Levobupivacaine; bupivacaine.

How to cite this article:

Gurpreet Singh, Niraj Mansukhlal Rathod, Kirti Patel. Comparison of Equipotent Doses of Hyperbaric Ropivacaine and Hyperbaric Levobupivacaine in Spinal Anaesthesia for Patients Undergoing Lower Abdominal and Lower Limb Surgeries. Indian J Anesth Analg. 2019;6(1):249-54.

Introduction

Spinal anaesthesia was introduced in clinical practice by Karl August Bier, in 1898 [1]. it is obtained by administering local anaesthetic agents in the subarachnoid space and thereby blocking nerves. Subarachnoid block is usually performed for lower abdominal and lower limb surgeries.

Corresponding Author: Niraj Mansukhlal Rathod, Assistant Professor, Department of Anesthesia, SBKS Medical Institute and Research Centre, Pipariya, Vaghodiya, Vadodara, Gujarat 391760, India.

E-mail: drnmrathod@gmail.com

Received on 22.12.2018, **Accepted on** 03.01.2019

It provides sensory as well as motor blockade. Levobupivacaine, an amide local anesthetic, is an S-enantiomers of racemic bupivacaine. On a per-milligram basis, it is less cardio toxic than bupivacaine, as it has decreased potency at the sodium channel. Studies have suggested that it has equivalent clinical efficacy to bupivacaine [6]. Ropivacaine is another amino-amide local anesthetic (LA) agent that is similar in chemical structure to bupivacaine, but it is 30-40% less potent than bupivacaine. Intrathecal Ropivacaine is safe, has shorter duration of action than bupivacaine and lesser incidence of transient neurological symptoms (TNS) as compared with intrathecal lignocaine.

In this study, we evaluated and compared the influence of hyperbaric Levobupivacaine and hyperbaric Ropivacaine on onset, duration of motor and sensory blockade, the incidence of side effects and complications particularly bradycardia, hypotension, fall of mean arterial pressure etc for spinal anaesthesia in patients undergoing lower abdominal and lower limb Surgeries.

Materials and Methods

This prospective, interventional, double blind study included sixty patients who were scheduled for lower abdomen and lower limb surgery under spinal anesthesia whose consents were taken. A detailed pre-anaesthetic check-up was done a day prior to surgery. In pre-induction phase details like temperature, pulse, blood pressure, respiratory rate, oxygen saturation (SpO_2), intravenous line, details of pre medication and pre-loading were captured.

Inclusion criteria: Patients of either gender aged between 20-60 years, Scheduled for surgery to be performed under spinal anaesthesia, Patient with American Society of anaesthesiologists grade-I and II (ASA I & II), Weight: 40-80 kg, No known history of drug allergy, sensitivity or history of other form of reaction.

Exclusion criteria: Patient with ASA III or IV, Patients with history of coagulopathy. Patients with spine deformity. Patients with local skin infections at the site of injection. Patient having fever, history of drug allergy. Patients who had shivering even before administering spinal anaesthesia Patients requiring supplementation with general anaesthesia Patients who were not willing to participate in the study.

Investigational medicinal product details

Study drug 1: Hyperbaric Ropivacaine

Study drug 2: Hyperbaric Levobupivacaine

Preparation of equipotent doses of hyperbaric Levobupivacaine and Ropivacaine: Various studies suggest that Ropivacaine is less potent than Levobupivacaine because of its lower lipid solubility, however using an equipotency ratio 1.5:1 between Ropivacaine and Levobupivacaine results in substantially similar in clinical profile. On the day of the surgery, patients were randomly assigned by computer generated randomisation table to either of the two arms mentioned below:

Group – R–Hyperbaric Ropivacaine [0.75% Ropivacaine (3 ml) + 25% dextrose(1 ml) (Total 4 ml)]

Group–L –Hyperbaric Levobupivacaine [0.5% Levobupivacaine (3 ml) + 25% dextrose (1 ml) (Total 4 ml)]

Dosage: 3.5 ml of the prepared solution was injected in each of the groups.

Procedure for study drug administration

All the patients were kept nil by mouth for more than 6 hours, i.e. were fasted preoperatively since 10 pm, night before surgery. All the patients were pre medicated with Inj. Ondansetron 4 mg and Inj. Ranitidine 50 mg and inj. Glycopyrrolate 0.2 mg intravenously. On the day of surgery the patients were brought to the operation theatre (OT), standard monitors (that measure pulse, blood pressure, Respiratory rate, Oxygen saturation) were attached and baseline parameters recorded. Patients were pre-loaded with ringer lactate 10 ml/kg and spinal anaesthesia performed. Efficacy / safety assessment was performed by investigator, who was blinded to study treatment allocation.

Efficacy (Onset of the Sensory and Motor Block) / Safety Assessment

Sensory block assessment - It was tested by pin prick using hypodermic needle.

Following parameters were recorded: Time of onset (time of intrathecal injection of drug to achieve T10 segment level block) Highest level of sensory blockade, Time for two segment regression of sensory level, Duration of sensory block (time period from onset of block to the time of two segment regression from T10).

Motor block assessment- It was tested using Bromage scale.

Following parameters were recorded: Time of onset (when Bromage scale 3 ie. patient is unable to move the hip, knee and ankle joint is achieved), Degree of motor blockade

Duration of motor blockade were recorded (time

period from onset to Bromage scale 0 ie. patient is able to move the hip, knee and ankle joint).

Intra-Operative Patient Monitoring: All patients of both groups were monitored for: Systolic and Diastolic blood pressure & Pulse rate (Haemodynamic parameters) Arterial oxygen saturation (SpO2) and Respiratory rate Side effects and complications (if any). Decrease in systolic arterial pressure (SAP) by more than 20% from the pre-anaesthetic value or decrease of patients' mean arterial pressure (MAP)to below 60 mmHg were considered to be suggestive of significant hypotension and were managed using injection Mephentermine 6 mg in increments intravenously along intravenous fluid replacement. Significant bradycardia (HR <60 beats/min) was treated with inj. atropine sulphate 0.6 mg intravenously.

Results

The data were analyzed using SPSS software version 18.0. Statistical analysis of data among groups was done, performed by

- Nominal data (such as Age groups) were presented as number and Percents.
- Continuous data (such as age, lab values) were expressed as mean, standard deviation and range.
- *'f' test and 't' test* was applied as appropriate for comparison of continuous data.
- *'Chi' test* was applied as appropriate for comparison of nominal data.
- '*p*' value of 0.05 was considered as statistically significant. (Confidence interval of 95% was taken into account).

In the present study, a total of 60 patients with ASA grading II and III undergoing lower abdominal surgery were enrolled. Equal number of patients were randomized in group- L (those who received levobupivacaine as spinal anesthesia) (n=30) and group – R(those who received ropivacaine as spinal anesthesia) (n=30).

Table 1: Comparison of time of onset of motor block in both the groups

Study groups		Time of onset of motor block (minutes)	P-value	Remarks
Group-L	Mean	25.07	>0.05	NS
	SD	1.97		
Group-R	Mean	24.37		
	SD	1.70		

Time of onset of motor block was compared in both the groups. It was seen that mean time to onset of motor block was 25.07±1.97minutes in group-L and 24.37±1.70 minutes in group-R. The difference was not clinically significant (Table 1).

Table 2: Comparison of average duration of motor blockade in both the groups

Study groups		Duration of motor blockade (Minutes)	P-value	Remarks
Group-L	Mean	116.73	>0.05	NS
	SD	29.95		
Group-R	Mean	112.93		
	SD	15.40		

Average duration of motor block was compared in both the groups. It was seen that average duration of motor block was 116.73±29.95 minutes in group-L and 112.93±15.40 minutes in group-R. The difference was not clinically significant (Table 2).

Table 3: Time of onset of Sensory block (Minutes)

Study Groups		Time of onset of Sensory block (Minutes)		
Group-L	Mean	17.07	>0.05	NS
	SD	1.93		
Group-R	Mean	15.5		
	SD	1.81		

Time of onset of sensory block was compared in both the groups. It was seen that mean time to onset of sensory block was 17.07±1.93 minutes in group-L and 15.5±1.81 minutes in group-R. The difference was not clinically significant (Table 3).

Table 4: Time to highest level of Sensory block (Minutes) in both the groups

Study Group		Time to highest level of sensory blockade minutes	P value	Remarks
Group-L	Mean	22.07	<0.05	S
	SD	1.93		
Group-R	Mean	20.5		
	SD	1.81		

Time to highest level of sensory block was compared in both the groups. It was seen that mean time to attain highest level of sensory block was 22.07±1.93 minutes in group-L and 20.5±1.81 minutes in group-R. The difference was clinically significant (Table 4).

Table 5: Time to two segment regression of sensory level (Minutes) in both the groups

Study group		Time to two segment regression of sensory level (minutes)	P-value	Remarks
Group-L	Mean	69	<0.05	S
	SD	8.5		
Group-R	Mean	61.83		
	SD	6.31		

Time to two segment regression of sensory block was compared in both the groups. It was seen that mean time to two segment regression of sensory block was 69±8.5 minutes in group-L and 61.83±6.31 minutes in group-R. The difference was clinically significant (Table 5).

Table 6: Duration of sensory block (Minutes) in both the groups

Study group		Duration of sensory block (minutes)	P-value	Remarks
Group-L	Mean	188.73	>0.05	NS
	SD	29.94		
Group-R	Mean	192.2		
	SD	36.01		

Average duration of sensory block was compared in both the groups. It was seen that average duration of sensory block was 188.73±29.94 minutes in group-L and 192.2± 36.01 minutes in group-R. The difference was not clinically significant (Table 6).

Discussion

Literature, suggest that ropivacaine on a molar to molar basis is considered to be less potent than levobupivacaine due to lower lipid solubility, and thereby using an equipotency ratio of 1.5:1 between ropivacaine and levobupivacaine provides nearly similar efficacy outcome [9]. etron. This study was conducted to compare the efficacy and safety profile of equipotent doses of levobupicaine and ropivacaine in patients undergoing lower limb and lower abdominal surgeries. Current study was conducted in 60 patients aged between 20 and 60 years having ASA grade I or II and scheduled for elective lower abdominal surgeries under spinal anaesthesia. Group L (Levobupivacaine group) – received hyperbaric levobupivacaine [0.5% Levobupivacaine (3 ml) + 25% dextrose (1ml) (Total 4 ml)].

Group R (Ropivacaine group) – received hyperbaric ropivacaine [0.75% Ropivacaine (3 ml) + 25% dextrose (1 ml) (Total 4 ml)] the following parameters were observed:

1. Time of onset (time of intrathecal injection of drug to achieve T10 segment level block)
2. Time to highest level of sensory blockade,
3. Time for two segment regression of sensory level
4. Duration of sensory block (time period from onset of block to the time of two segment regression from T10)
5. Time of onset (when Bromage scale 3 ie. patient is unable to move the hip, knee and ankle joint is achieved)
6. Duration of motor blockade were recorded (time period from onset to Bromage scale 0 ie. patient is able to move the hip, knee and ankle joint)

In our study the mean time of onset of motor block was 25.07±1.97 minutes in group-L and 24.37 ±1.70 minutes in group-R and the difference was not clinically significant. This was similar to the findings by Suri A et al., where in the mean onset of time of motor block was 24.09±3.07 vs 25.47±4.13 minutes in group L and group R and the difference was not clinically significant (p = 0.076) [26]. However, the mean time of onset of motor block in study by Mantouvalou M et al. was 12±5 min in the ropivacaine group (group B) and 11±7 min in the levobupivacaine group, the early onset in this study as compared to our study may be due to the fact that, Mantouvalou M et al. used isobaric preparation in their study which may have resulted in rapid intrathecal spread [24]. Additionally, the mean age of the patients in the study by Mantouvalou M et al. was higher compared to our study and as per literature at the extremes of age there are small but significant increases in maximum spread, rate of onset of motor block and cardiovascular instability, regardless of the solution used [3]. Luck JF in their study observed that mean time to maximum motor block was 5 (2–20) and 10 (5–20) (min) in levobupivacaine and ropivacaine group respectively [22]. The early onset seen in Luck JF study may have been due to the fact that the mean age of the patients enrolled in the study was 57 (26–73) and 59 (37–75) in group L and R respectively which was higher compared to our study.

The average duration of motor block in the current study was 116.73±29.95 minutes in group-L and 112.93±15.40 minutes in group-R. Similar findings were seen in the published literature, although Mantoualou M et al. have observed significantly higher duration of motor block, authors have offered no explanation for the same (Table 7).

In the current study time of onset of sensory block was 17.07±1.93 minutes in group-L and 15.5

±1.81 minutes in group-R. The results were similar to published literature (Table 8).

Time to highest level of sensory block was 22.07 ±1.93 minutes in group-L and 20.5±1.81 minutes in group-R. The results were similar to published literature (Table 9).

Time to two segment regression of sensory block was 69±8.5 minutes in group-L and 61.83±6.31 minutes in group-R. The results were similar to published literature (Table 10).

Average duration of sensory block was 188.73 ± 29.94 minutes in group-L and 192.2±36.01 minutes in group-R. The results were similar to published literature (Table 11).

In the current study he mean duration of post-operative analgesia was 137.70±28.01 minutes in Group L and 131.2±38.97 minutes in Group R. The results were similar to published literature (Table 12).

Conclusion

From the present prospective, interventional, double blind study of intrathecal equipotent doses of Ropivacaine and Levobupivacaine, it can be concluded that Ropivacaine is reliable and safe alternative to Levobupivacaine and can be used interchangeably. Hyperbaric Ropivacaine can be specifically used for population that is at higher risk

Table 7: Comparison of average duration of motor block of current study with literature

	Average duration of motor block (Minutes)				
Literature	**Current study**	**Suri A et al. [26]**	**Gautier P et al. [17]**	**Luck JF et al. [22]**	**Mantouvalou M et al. [24]**
Group-L	116.73±29.95	118.53±18.14	121±25	180 (90–210)	273±80
Group-R	112.93±15.40	111.42±16.70	116±19	90 (60–120)	269±20

Table 8: Comparison of time of onset of sensory block of current study with literature

	Mean time of onset of sensory block (Minutes)			
Literature	**Current study**	**Suri A et al. [26]**	**Luck JF et al. [22]**	**Khan A et al. [19]**
Group-L	17.07±1.93	18.62±3.09	5 (2–15)	9.66±1.99
Group-R	15.5±1.81	17.93±2.98	5 (2–15)	9.48±1.92

Table 9: Comparison of time to highest level of sensory block of current study with literature

	Mean time to highest level of sensory block (Minutes)			
Literature	**Current study**	**Gautier P et al. [17]**	**Luck JF et al. [22]**	**Mantouvalou M et al. [24]**
Group-L	22.07±1.93	17±9	25 (10–30)	11±6
Group-R	20.5±1.81	15±9	20 (2–30)	12±7

Table 10: Comparison to two segment regression of sensory block of current study with literature

	Time to two segment regression of sensory block (Minutes)			
Literature	**Current study**	**Mantouvalou M et al. [24]**	**Gautier P et al. [17]**	**Luck JF et al. [22]**
Group-L	69±8.5	65±11	69±14	131 (50–205)
Group-R	61.83±6.31	60±9	60±21	84 (45–145)

Table 11: Comparison average duration of sensory block of current study with literature

	Average duration of sensory block (Minutes)				
Literature	**Current study**	**Suri A et al. [26]**	**Gautier P et al. [17]**	**Khan A et al. [19]**	**Luck JF et al. [22]**
Group-L	188.73±29.94	189.0±19.53	124±24	175.38±13.60	255 (180–360)
Group-R	192.2±36.01	196.78±20.31	120±27	170.80±19.81	210 (180–330)

Table 12: Comparison mean duration of post-operative analgesia of current study with literature

	Mean duration of post-operative analgesia (Minutes)			
Literature	**Current study**	**Suri A et al. [26]**	**Gautier P et al. [17]**	**Khan A et al. [19]**
Group-L	188.73±29.94	253.78±24.43	140 (110-270)	190.27±18.61
Group-R	192.2 ± 36.01	263.0 ± 22.77	135 (95-175)	187.67±23.92

of cardiac toxicity, without compromising on time of onset or duration of motor and sensory blocks

References

1. Bier A. Versucheuber Kokainiserung des Ruchenmarkes (Experiments on cocaine rash). Dtsche Z Chir. 1899;51:361–9.
2. Bier A. On the current state of spinal anesthesia, its legitimacy, its advantages and disadvantages compared to other methods of anesthesia. Langenbeck's Archiv fur Klinische Chirurgie. 1905; 77:198-208.
3. G. Hocking, J.A.W. Wildsmith. Intrathecal drug spread. British Journal of Anaesthesia. 2004;93(4):568–78.
4. Barker AE. Clinical experiences with spinal analgesia in 100 cases. Br Med J 1907;1:665.
5. Pitkin GP. Spinocain: the controllable spinal anaesthetic. Br Med J. 1929;2:189.
6. McLeod GA, Burke D. Levobupivacaine. Anaesthesia. 2001 Apr;56(4):331-41
7. Kulkarni KR et al. A comparative evaluation of hyperbaric ropivacaine versus hyperbaric bupivacaine for elective surgery under spinal anesthesia. Journal of Anaesthesiology Clinical Pharmacology. 2014 April-June:30(2);238-42.
8. Clinical trial NCT03142880. Spinal Marginally Hyperbaric Ropivacaine for Cesarean Delivery. https://clinicaltrials.gov/ct2/show/NCT03142880
9. Stefania Leone, Stefania Leone, Simone Di Cianni, Andrea Casati, Guido Fanelli Pharmacology, toxicology and clinical use of new long acting local anesthetics, ropivacaine and levobupivacaine. Acta Biomed 2008;79:92-105.
10. Looseley A. Corning and cocaine: the advent of spinal anaesthesia. Grand Rounds. 9;L1–L4.
11. Calatayud J, González Á. History of the Development and Evolution of Local Anesthesia Since the Coca Leaf. Anesthesiology. 2003;98:1503–8.
12. Ruetsch YA, Böni T, Borgeat A. From cocaine to ropivacaine: the history of local anesthetic drugs. Curr Top Med Chem. 2001 Aug;1(3):175-82.
13. Casati A, Putzu M. Bupivacaine, levobupivacaine and ropivacaine: are they clinically different? Best Pract Res Clin Anaesthesiol. 2005 Jun;19(2):247-68.
14. Ang Li et al. Ropivacaine versus levobupivacaine in peripheral nerve block. Medicine. 2017;96:14.
15. Khairnar P et al. Comparative efficacy of ropivacaine and levobupivacaine in combined femoral and lateral femoral cutaneous nerve block with adjuvant magnesium for post-operative analgesia. Indian Journal of Anaesthesia. 2016 Aug;60(8):64-9.
16. Charles PD et al. 0.5% levobupivacaine versus 0.5% ropivacaine: Are they different in ultrasound-guided sciatic block?. Saudi Journal of Anesthesia. 2015 January-March;9(1):3-8.
17. P. Gautier, M. De Kock, L. Huberty, T. Demir, M. Izydorczic, B. Vanderick. Comparison of the effects of intrathecal ropivacaine, levobupivacaine, and bupivacaine for Caesarean section. British Journal of Anaesthesia. 2003;91(5):684-9.
18. Hanna M, Sloan P. A Comparison of Levobupivacaine and Ropivacaine for Interscalene and Femoral Nerve Blocks: A Randomized, Double-Blind, Prospective Clinical Trial. J Anesthe Clinic Res. 2011;2:135.
19. Khan A, Nanda H S, Chandra R. Levobupivacaine versus Ropivacaine: A Comparative Study of the Analgesic and Hemodynamic Spectrum. Int J Sci Stud. 2016;4(1):190-195.
20. Khaw KS, NganKee WD, Wong M, Ng F, Lee A. Spinal ropivacaine for cesarean delivery: a comparison of hyperbaric and plain solutions. AnesthAnalg. 2002 Mar;94(3):680-5.
21. P. Gautier, M. De Kock, L. Huberty et al. Comparison of the effects of intrathecal ropivacaine, levobupivacaine, and bupivacaine for Caesarean section. British Journal of Anaesthesia. 2003;91(5):684-9.
22. Luck JF, Fettes PDW, Wildsmith JAW. Spinal anaesthesia for elective surgery: a comparison of hyperbaric solutions of racemic bupivacaine, levobupivacaine, and ropivacaine. British journal of Anaesthesia. 2008;101(5):705-10.
23. Gupta R et al. Comparative study of intrathecal hyperbaric versus isobaric ropivacaine: A randomized control trial. Saudi J Anaesth. 2013 Jul-Sep;7(3):249–53.
24. Mantouvalou M, Ralli S, Arnaoutoglou H, Tziris G, Papadopoulos G. Spinal anesthesia: Comparison of plain ropivacaine, bupivacaine and levobupivacaine for lower abdominal surgery. ActaAnaesth. Belg. 2008;59:65-71.
25. Bigat Z, Boztug N, Karsli B, Cete N, Ertok E. Comparison of hyperbaric ropivacaine and hyperbaric bupivacaine in unilateral spinal anaesthesia. Clin Drug Investig. 2006;26(1):35-41.
26. A Suri, G Sindwani, R Mane. Comparison of onset and duration of sensory and motor blockade between equipotent doses of 0.75% plain ropivacaine and 0.5% plain levobupivacaine in lower abdominal surgeries under epidural anaesthesia - A one year hospital based randomized clinical study.
27. Greene NM. Distribution of local anesthetic solutions within the subarachnoid space. AnesthAnalg. 1985; 64:715–30.

Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(1) (Part - II): 255-62
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.36

Role of Intravenous Paracetamol for Peri-Operative Pain Management in Head and Neck Cancer Surgeries

Jayshree M Thakkar[1], Anupama Tomer[2], Priti M Patel[3]

[1]Associate Professor, [2]Ex Resident, [3]Assistant Professor, Department of Anaesthesia, Gujarat Cancer and Research Institute, Civil Hospital Campus, Asarwa, Ahmedabad, Gujarat 380016, India.

Abstract

Background: Inadequately controlled postoperative pain causes discomfort, increased use of medications, slower recovery, longer hospital stay and increased risk of pulmonary complications [5]. Postoperative analgesia with safer drugs and minimal side effects is the first choice. This study was undertaken to evaluate the role of Inj. Paracetamol vs. Inj. Tramadol in post-operative pain relief after head and neck cancer surgeries. *Material & Method:* After IRB approval and informed consent, this prospective, randomized study was conducted in 100 patients (ASA I & II) with age group of 18-60 years undergoing elective head and neck cancer surgery. Patients were divided into two groups. A) Group P: Inj. Paracetamol 15 mg/kg IV over 15 min, 30 min prior to the end of surgery and subsequent doses at 6 hours interval 24 hours. B) Group T: Inj. Tramadol 1 mg/kg diluted in 10 ml saline IV slowly over 10 min, 30 min prior to end of surgery and subsequent doses at 8 hours interval for 24 hours. *Results:* Postoperative VAS decreased at various time intervals in both groups. Time to 1st dose of rescue analgesia requirement was lower in Group T, with mean postoperative rescue analgesic free time interval of 6.23±1.72 hours as compared to Group P where it is 5.01±1.16 hours. Frequency of rescue analgesic requirement was lower in Group T, with mean of 1.20 (±0.41), in comparison to Group P 1.67 (±0.71). Postoperative nausea, vomiting is more in group Tas compared to group P. *Conclusion:* Intravenous paracetamol administration in peri-operative period provided adequate postoperative analgesia with fewer side effects in patients undergoing head and neck cancer surgery. Intraoperative IV paracetamol appears to be a reasonable choice for postoperative analgesia in this patient population.

Keywords: Pain; Paracetamol; Tramadol.

How to cite this article:

Jayshree M Thakkar, Anupama Tomer, Priti M Patel. Role of Intravenous Paracetamol for Peri-Operative Pain Management in Head and Neck Cancer Surgeries. Indian J Anesth Analg. 2019;6(1):255-262.

Introduction

The word "pain'' has been derived from the Latin word "poena'' for punishment [1]. The International Association for the Study of Pain defines pain as an "unpleasant sensory and emotional experience associated with actual damage or potential tissue damage or described in terms of such damage" [2]. The Joint Commission on Accreditation of Healthcare Organizations has coined the phrase "Pain: The 5th Vital Sign" to elevate awareness of pain treatment among health care professionals [3].

Pain, a common presenting feature of many disease processes, is usually associated with

Corresponding Author: Anupama Tomer, Ex Resident, Department of Anesthesia, Gujarat Cancer and Research Institute, Civil Hospital Campus, Asarwa, Ahmedabad, Gujarat 380016, India.

E-mail: dr.anupama.tomer@gmail.com

Received on 20.11.2018, **Accepted on** 13.12.2018

actual or impending tissue damage. Acute pain in perioperative setting is defined as pain that is present in a surgical patient because of pre-existing disease, surgical procedure or a combination of these. It is an unpleasant and inevitable component of the postsurgical experience. It also exerts deleterious effects on systems like respiratory, cardiovascular, neuroendocrine, gastrointestinal and other systems of the body [4].

Inadequately controlled postoperative pain causes discomfort, increased use of medications, slower recovery, longer hospital stay and increased risk of pulmonary complications [5]. Postoperative analgesia with safer drugs and minimal side effects is the first choice.

NSAIDs, opioids and acetaminophens are used to alleviate postoperative pain. NSAIDs are associated with risk of bleeding and renal dysfunction while opioids are associated with potentially harmful effects like respiratory depression, post operative nausea and vomiting (PONV), sedation etc [6]. Acetaminophens are nowadays used for postoperative analgesia because of its well established safety and analgesic profile without significant drug interaction. Hepatic toxicity is rare but can occur with its overdose.

Paracetamol is commonly used drug for the treatment of pain and fever. Intravenous paracetamol crosses blood brain barrier easily and its analgesic action starts within 15-20 min. Maximal analgesic activity occurs 1-2 hours after peak plasma levels and peak plasma concentration is achieved approximately 25 min after 1 gm of IV infusion of paracetamol. Adverse reactions occurring from the use of IV paracetamol are extremely rare (1/1000).

Tramadol is a centrally acting analgesic. It has effect on norepinephrine and 5- hydroxytryptamine neurotransmitters. It has weak opioid agonist properties. Onset of IV formulation is within 5 min, analgesic effect peaks within 15 min and last for 4-6 hours.

This study was undertaken to evaluate the effect of two different drugs Inj. Paracetamol vs. Inj. Tramadol in terms of post-operative pain relief, hemodynamic stability and side effects after head and neck cancer surgeries.

Material and Methods

After institutional review board approval and informed consent, the study was conducted in 100 patients belonging to both sexes in the age group of 18-60 years with ASA physical status I & II, undergoing elective head and neck cancer surgery. Patients excluded were those with known allergy or hypersensitivity to paracetamol or tramadol, patients with history of alcohol, coagulopathy, and impaired liver and renal function. Patients were assessed in the preoperative visit and routine general and systemic examination was done. Preoperative vital parameters were noted. Patients were kept nil by mouth after 10 PM on the previous night before operation.

Patients were divided into two groups: Group P (Paracetamol): Inj Paracetamol 15 mg/kg IV over 15 minutes and 30 minutes prior to the end of surgery and subsequent doses at 6 hours intervals for 24 hours. Group T (Tramadol): Inj Tramadol 1 mg/kg diluted in 10 ml saline IV slowly over 10 minutes and 30 minutes prior to the end of surgery and subsequent doses at 8 hours interval for 24 hours.

After taking patient on the OT table, IV line was established and monitoring in the form of ECG, HR, NIBP, SpO_2 and $EtCO_2$ was done. Patients were pre-oxygenated with 100% O_2 for 3 minutes and general anaesthesia was administered with Inj Glycopyrolate 0.04 mg/kg + Inj Fentanyl 2 µg/kg + Inj Thiopentone Sodium (2.5%) 5 mg/kg and intubation was facilitated using Inj Succinylcholine HCL 2 mg/kg IV. Patients were intubated with appropriate size portex cuffed endotracheal tube. Bilateral air entry was checked and tube was fixed. Anesthesia maintained with O_2, N_2O, Isoflurane with controlled ventilation using Inj Vecuronium bromide 0.08 mg/kg IV. Intraoperative HR, BP, SpO_2, ECG and $EtCO_2$ were monitored. All the study drugs namely Paracetamol and Tramadol were given as described above to two groups of 50 patients each. After completion of surgery, neuromuscular blockade was reversed with Inj Glycopyrrolate 0.08 mg/kg and Inj Neostigmine 0.05 mg/kg IV. Extubation was done after adequate oropharyngeal and endotracheal suctioning when they were fully conscious.

In the postoperative period vital parameters heart rate (HR), systolic & diastolic blood pressure (SBP) (DBP) and pain score (VAS) (0-10) were assessed and documented at 0 min, 3, 6, 9, 12, 16, 20 and 24 hours intervals.

If VAS > 4, rescue analgesic Inj. Tramadol 1 mg/kg IV was given. Need of rescue analgesia in 24 hours was assessed and documented.

Adverse effects like nausea, vomiting, respiratory depression, abdominal pain, allergic reactions, alteration in liver function tests within 24 hours of surgery were assessed and documented in both

the study drug groups. Ondansetron 4 mg IV was administered if patient experienced severe nausea and episode of vomiting.

Results

This study was a prospective, randomized one. The total number of 100 patients, who were posted for head and neck cancer surgeries, were enrolled in the study. The data was recorded in Excel panel and statistical analysis was done after completion of the study. Data was analyzed by standard statistical unpaired t-test using Graph pad software and for significant difference between the groups, p-value of < 0.05 was taken as a reference of significance.

Table 1 shows demographic details. Mean age (yr) and wt (kg) in both the groups are comparable and statistically not significant ($p > 0.05$). Mean surgical duration in both groups is statistically not significant ($p > 0.05$).

Table 2 shows heart rate changes in both groups at different intervals**.** Changes in heart rate between the two groups at different intervals were not significant and were statistically comparable in both the groups. Heart rate was on the higher side just after the recovery from anesthesia with a mean value of 87.34 (±4.03) in Group P and 86.68 (±3.28) in Group T and their P value is 0.3713 that is insignificant, but after 3 hours interval, there is mild decrease in the values for heart rate with highest value reaching in Group P is 78.88 (±2.45), and in Group T, it is 78.64 (±2.31), which are statistically insignificant.

Table 3 shows systolic blood pressure changes in both groups at different intervals. Changes in systolic blood pressure at different intervals between the two groups were not significant and were statistically comparable in both the groups. Highest mean value of SBP was 131.74 (±4.47) mm of Hg in Group P and 130.88 (±4.37) mm of Hg in Group T, are statistically insignificant on comparison with a p value > 0.05.

Table 4 shows diastolic blood pressure changes in both groups at different intervals. Changes in diastolic blood pressure at different intervals between the two groups were not significant and were statistically comparable in both the groups. There is no significant variation in both the groups at different intervals, with highest mean value of 86.26 (±2.55) mm of Hg in Group P and 85.66 (±1.72) mm of Hg in Group T, are statistically insignificant on comparison with a P value > 0.05.

Table 5 shows visual analogue score (VAS) at different intervals. VAS was significantly lower at certain time intervals in both the groups. First analgesic time was longer in the Tramadol group as compared to Paracetamol group. Mean VAS was statistically comparable in the immediate postoperative period with a p-value of 0.3953 which is insignificant. At an interval of 3 hours, the mean VAS is 3.10 (±0.51) in Group P and it is 2.94 (±0.24) in Group T and they are statistically significant (P=0.0458). But after 6 hours interval, the mean VAS decreased to 0.88 (±0.59) in Group P and it is increased to 3.84 (±1.47) in Group T, which is statistically significant (p<0.0001). This indicates that after administration of subsequent

Table 1: shows Demographic Data

Variables	Group P	Group T	p value	Significance
Age (Years)	48.40±12.18	48.04±10.70	0.8756	NS
Weight(kgs)	60.18±6.48	58.96±5.37	0.3079	NS
Sex (M/F)	39/11	40/10	-	-
ASA status(I/II)	24/6	25/5	-	-
Duration of surgery(mins)	210.83±41.83	219.33±47.32	0.7434	NS

Table 2: shows Heart rate changes (BPM) in both groups at different intervals

Time	Group P (Mean±Sd)	Group T (Mean±Sd)	p Value
00 min	87.34±4.03	86.68±3.28	0.3713
03 hrs	81.94±2.66	81.80±2.64	0.7922
06 hrs	78.88±2.45	78.64±2.31	0.6154
09 hrs	75.50±2.45	75.52±2.20	0.9658
12 hrs	73.84±1.87	73.90±1.64	0.8649
16 hrs	73.22±1.45	73.10±1.39	0.6736
20 hrs	72.74±1.06	72.60±1.07	0.5125
24 hrs	72.54±0.91	72.48±0.84	0.7326

dose of paracetamol in Group P patients, the mean VAS score decreased significantly, whereas it is on higher side in Group T patients in whom next dose was due at that time.

Table 6 shows rescue analgesic requirement in both the groups. Time to 1st dose of rescue analgesia requirement was lower in Group T in the 24 hours study period, with the mean postoperative rescue analgesic free time interval of 6.23±1.72 hours, as compared to Group P where it is 5.01±1.16 hours. This is found to be statistically significant with p-value of 0.0001.

Frequency of rescue analgesic requirement was lower in Group T in the 24 hours study period. Patients in Group T required 1 to 2 times of rescue analgesia with a mean of 1.20 (±0.41), in comparison to the Group P, where patients required 2 to 3 times of rescue analgesia with a mean of 1.67 (±0.71). However, this was also found to be statistically significant with p value of 0.001.

Table 3: Shows SBP changes (mm of Hg) in both groups at different intervals

Time	Group P(Mean±Sd)	Group T(Mean±Sd)	p Value
0 min	131.74±4.47	130.88±4.37	0.3331
3 hrs	128.02±4.11	127.58±3.96	0.5869
6 hrs	125.78±3.09	125.04±2.43	0.1862
9 hrs	123.52±2.13	123.14±1.78	0.3354
12 hrs	121.95±1.93	121.52±1.62	0.2305
16 hrs	120.54±1.82	119.86±1.68	0.0551
20 hrs	119.42±1.57	118.94±1.38	0.1076
24 hrs	117.98±1.67	117.52±1.53	0.1542

Table 4: Shows DBP changes (mm of Hg) in both groups at different intervals

Time	Group P (Mean±Sd)	Group T (Mean±Sd)	p Value
00 min	86.26±2.55	85.66±1.72	0.1709
03 hrs	82.80±2.29	82.36±1.85	0.2932
06 hrs	82.14±2.14	81.68±1.73	0.2401
09 hrs	81.62±1.88	80.96±1.71	0.0693
12 hrs	80.70±1.53	80.02±2.06	0.0639
16 hrs	79.68±1.43	78.98±2.08	0.0527
20 hrs	78.84±1.31	78.48±2.05	0.2980
24 hrs	76.72±1.75	76.10±2.00	0.1022

Table 5: shows Visual Analogue Score (VAS) at different intervals

Time	Group P (Mean±Sd)	Group T (Mean±Sd)	p Value
0 min	2.12±0.39	2.06±0.31	0.3953
3 hrs	3.10±0.51	2.94±0.24	0.0458
6 hrs	0.88±0.59	3.84±1.47	<0.0001
9 hrs	3.04±0.28	2.06±0.31	<0.0001
12 hrs	1.98±0.44	3.62±0.98	<0.0001
16 hrs	3.08±0.74	1.76±0.46	<0.0001
20 hrs	2.12±0.38	2.10±0.51	0.8243
24 hrs	0.88±0.59	0.76±0.48	0.2678

Table 6: shows Rescue analgesic requirement

Rescue analgesia	Group P	Group T	p Value
Time to 1st dose of rescue analgesia (hrs)	5.01±1.16	6.23±1.72	0.0001
Total no of doses of rescue analgesic in 24 hrs	1.67±0.71	1.20±0.41	0.001

Table 7: shows Side Effects

Side Effects	Group P	Group T
Sedation	nil	3
Abdominal pain	nil	nil
LFT complications	nil	nil
Nausea & vomiting	5	16
Respiratory depression	nil	nil
Allergic reaction	nil	nil

Table 7 shows side effects in both the groups**.** Group P recorded less number of patients (10%) with nausea and vomiting (PONV) as compared to Group T which recorded significantly higher number of patients (32%) in the immediate post-operative period. Also, sedation was seen in 3 patients (6%) in Group T. No alterations were seen in the liver function tests of the patients receiving paracetamol.

Discussion

Pain is a subjective and multidimensional experience that is often inadequately managed in clinical practice. It is a multifaceted and highly personal experience, as McCaffery described "pain is whatever the experiencing person says it is and exists whatever he/she says it does" [7]. It causes significant distress to patients and has adverse effects on the endocrine and immune system function, which can affect wound healing and cardiopulmonary and thromboembolic diseases. Post-operative pain is one of the most frequently reported post-operative symptoms. The post-operative period was defined as the period between arrivals of the patient in recovery to 7 days after surgery, with day 1 being 24 hours after surgery. The incidence of moderate to severe pain with cardiac, abdominal or orthopedic inpatient procedures has been reported to be as high as 25% to 76% [8].

Management of post-operative pain in the initial 24 hours is critical. Inadequate pain management leads to delayed mobilization and longer duration of stay in the hospital. Post-operative pain is an unpleasant sensory, emotional and mental experience which is precipitated as a result of surgery and is often associated with autonomic, endocrine, metabolic, physiological and behavioral response.

With this background, we designed the study to compare the post-operative analgesic effects of intravenous paracetamol and intravenous tramadol in head and neck cancer surgery patients. Analgesic effects were assessed with Visual Analogue Scale (VAS Score) in both the groups.

In our study, we have found that there was no significant variation between the groups when comparing the demographic variables like age, sex, weight, ASA status and the duration of surgeries. Premedication and anaesthetic technique was kept constant in order to avoid variations in our observations.

While comparing the heart rate, we found that there was no statistically significant variation in both the groups. Heart rate was on the higher side just after the recovery from anaesthesia with a mean value of 87.34 (±4.03) in Group P and 86.68 (±3.28) in Group T and their P-value is 0.3713 that is insignificant, but after 3 hours interval, there is mild decrease in the values for heart rate with highest value reaching in Group P is 78.88 (±2.45), and in Group T, it is 78.64 (±2.31), which are statistically insignificant. So, we can correlate the initial increase in heart rate is due to anxiety and not due to pain. Mean changes in heart rate at different intervals are insignificant.

Mohammed Shahid et al. [9] (2015), in their comparative study of intravenous paracetamol and intravenous tramadol for postoperative analgesia in laparotomies found that nothing statistically significant was observed in terms of hemodynamics including VAS scores between either group. They said that IV paracetamol is a safer alternative to tramadol with lesser PONV in the postoperative period which results into the lesser duration of hospitalization and hence earlier discharge.

Pratyush Goel et al. [5] in their comparative study for pre-emptive analgesia with IV paracetamol and IV diclofenac sodium in patients undergoing various surgical procedures found the comparison of heart rate between paracetamol and diclofenac group was significant. Heart Rate was almost equal to base line value in Diclofenac group patients and it was increased in paracetamol group patients. Mean values of SBP and DBP showed increase in Paracetamol group however it was not significant.

While comparing SBP, we found that changes in SBP in both the groups at different intervals, with highest mean value of 131.74 (±4.47) in Group P and 130.88 (±4.37) in Group T, are statistically insignificant on comparison with a p value > 0.05.

While comparing the DBP, in both the groups, we have observed that there is no significant variation in both the groups at different intervals, with highest mean value of 86.26 (±2.55) in Group P and 85.66 (±1.72) in Group T, are statistically insignificant on comparison with a p value > 0.05.

Arici et al. [10] studied the pre-emptive analgesic effects of intravenous paracetamol in total abdominal hysterectomy and found a decrease in mean values of heart rate, SBP, DBP intra-operatively after paracetamol administration. They also found decrease consumption of morphine post-operatively.

In this study, the mean VAS was statistically comparable in the immediate postoperative period with a p-value of 0.3953 which is insignificant. At 3 hours, the mean VAS is 3.10 (±0.51) in Group P and it is 2.94 (±0.24) in Group T and they are statistically significant (P=0.0458). But after 6 hours interval, the mean VAS is decreased to 0.88 (±0.59) in Group P and it is increased to 3.84 (±1.47) in Group T, which is statistically significant (p<0.0001). This indicates that after administration of subsequent dose of paracetamol in Group P patients, the mean VAS decreased significantly, whereas it is on higher side in Group T patients in whom next dose was due at that time.

Nikoda et al. [11] in his study of IV infusion of paracetamol in a single dose of 1g (4 g/day) for postoperative analgesia reported a reduction in the intensity and duration of pain and that the IV formulation of paracetamol should be used as multimodal therapy for mild to moderate postoperative pain management.

At 9 hours, the mean VAS is 3.04 (±0.28) in Group P and it is 2.06 (±0.31) in Group T, which is statistically significant (p<0.0001). And at 12 hours, the mean VAS is 1.98 (±0.44) in Group P and it is 3.62 (±0.44) in Group T, which is statistically significant (p < 0.0001). Again at 16 hours, the mean VAS is 3.08 (±0.74) in Group P and it is 1.76 (±0.46) in Group T. There is higher VAS score in Group P as compared to Group T, which is statistically significant (p < 0.0001). This indicates that after administration of subsequent doses of either paracetamol or tramadol, the pain relief is adequate, which is seen in decline in respective mean VAS score in both the groups.

After 20 hours in post-operative period, the mean VAS is 2.12 (±0.38) in Group P and it is 2.10 (±0.51) in Group T, which is statistically insignificant (p=0.8243). And at 24 hours, the mean VAS is 0.88 (±0.59) in Group P and it is 0.76 (±0.48) in Group T, which is also statistically insignificant (p=0.2678).

Sinatra RS et al. [12] in his study found that intravenous acetaminophen was consistently superior to placebo for pain relief and for pain intensity changes from 15 min to 6 h after the first dose and throughout the 24-h evaluation period after repeated dose administration. Jeong-Yeon Hong et al. [6] showed that VAS scores were significantly lower in the paracetamol group at 1, 3, 6 and 24 hours after surgery and significantly fewer patients in the paracetamol group received rescue analgesic than the placebo group.

Aghamir et al. [13] compared propacetamol and tramadol after urologic open surgeries and found propacetamol useful, but inadequate in cases of severe pain, whereas Uysal et al. [14] compared either of the drugs in post-adenotonsillectomy pediatric patients and found iv paracetamol to be superior in terms of early recovery, but associated with similar analgesic properties. Turhan Togrul et al. [15] studied the comparison of intravenous Paracetamol and Tramadol for postoperative analgesia in patients with septo-rhinoplasty and concluded that iv paracetamol administration provided adequate analgesia as opioids especially at early post-operative period for mild to moderate pain therapy in peri-operative period. Howard S. Smith et al. [16] studied the analgesic effects of intravenous paracetamol and NSAIDs and concluded that iv paracetamol represents a safe and effective first-line analgesic agent for the treatment of acute mild-to-moderate pain in the perioperative setting.

Sinatra et al. [12] found that IV paracetamol has rapid onset of analgesia in orthopaedic surgeries and IV paracetamol 1 g administered in patients with moderate to severe pain offered quick and effective analgesia. They found IV paracetamol significantly reduced morphine consumption over the 24 hours period and safe in terms of clinical and laboratory examinations. Cade et al. [17] and Hein et al. [18] in their study did not found postoperative analgesic or opioid sparing effects with paracetamol after minor and major surgery and this might be due to the single injection of paracetamol which would not be expected to provide pain relief even after minor surgery hence in our surgery we used repeated injections of paracetamol to get the desired effect.

We observed that the time to 1st dose of rescue analgesia requirement was lower in Group T in the 24 hours study period, with the mean postoperative rescue analgesic free time interval of 6.23±1.72 hours, as compared to Group P where it is 5.01±1.16 hours. This is found to be statistically significant with P value of 0.0001. Party's et al. [5] in his study found mean duration of analgesia in

paracetamol group to be 4.27 hours and slightly higher 4.86 hours in Tramadol group.

Also, the frequency of rescue analgesic requirement was lower in Group T in the 24 hours study period. The patients in Group T required 1 to 2 times of rescue analgesia with a mean of 1.20 (±0.41), in comparison to the Group P, where patients required 2 to 3 times of rescue analgesia with a mean of 1.67 (±0.71).This was also found to be statistically significant with P-value of 0.001.

In our study, 5 patients complained for PONV in Group P and 16 patients in Group T. Also, 3 patients complained of sedation in Group T. No cases of urinary retention were observed in either group.

Kela et al. [19] compared the efficacy of either drug in the postoperative period in cardiothoracic surgery and found 10.0% of the subjects in paracetamol group and 13.3% of the subjects in tramadol group suffered nausea and vomiting which were comparable and difference was insignificant. Caken T et al. [20], Mohammad Shahid et al. [9], Pratyush Goel [5] et al. and Jeong-Yeon Hong et al. [6] in their study found decreased incidence of nausea and vomiting with the use of IV paracetamol which is similar to our study.

It becomes evident from this study that the paracetamol can be a good alternative to tramadol and thus can avoid the complications associated with non-steroidal anti-inflammatory drugs and opioids.

Potential limitation of the study are that IV paracetamol in head and neck cancer offers central analgesic effects but the anti-inflammatory effects, which is enhances analgesia in the early post-operative period is not possible. So moderate to severe pain and bony pain may not be addressed adequately with paracetamol. Though it is having less incidence of PONV than tramadol, patients with borderline liver dysfunction patients may be at high risk as only repeated administration of paracetamol is effective.

Conclusion

Intravenous paracetamol administration in peri-operative period provided adequate postoperative analgesia in patients undergoing head and neck cancer surgery. In contrast to opioids, paracetamol does not produce sedation, respiratory depression or constipation, nor is it associated with a risk of substance abuse or misuse. Based on these findings, intraoperative IV paracetamol appears to be a reasonable choice for postoperative analgesia in this patient population.

References

1. Lai DC. History of pain relief. In: Warfield CA, Fausett HJ. Manual of Pain Management: 2nd edition. Philadelphia: Lippincott Williams and Wilkins; 2002.p.3-5.
2. Suchdev PK. Pathophysiology of Pain. In: Warfield CA, Fausett HJ. Manual of Pain Management: 2nd edition. Philadelphia: Lippincott Williams and Wilkins; 2002.p.6-12.
3. Asdourian CP. Acute pain management. In: Warfield CA, Fausett HJ. Manual of Pain Management: 2nd ed. Philadelphia: Lippincott Williams and Wilkins; 2002.p.215-22.
4. James D, Justins D. Acute postoperative pain. In Thomas H, Knight PR, eds. Wylie's Textbook of Anesthesia, 7th Ed. 2003.pp.1213-34.
5. Pratyush Goel et al. Pre-emptive analgesia with IV paracetamol and IV diclofenac sodium in patients undergoing various surgical procedures: a comparative study. Int J Biol Med Res. 2013; 4(3):3294–3300.
6. Jeong-Yeon Hong, Won Oak Kim, WoongYoun Chung, Joo Sun Yun, and HaeKeumKil. Paracetamol Reduces Postoperative Pain and Rescue Analgesic Demand After Robot-Assisted Endoscopic Thyroidectomy by the Trans axillary Approach. World J Surg. 2010;34:521-26.
7. McCaffery M: pain: clinical manual for nursing practice, 2nd edition. Mosby, St. Louis, 1989: page 7.
8. Svensson, Sjostorm B. influences of expectations and actual pain experiences on satisfaction with postoperative pain management. Eur J Pain. 2001; 5:125-33.
9. Shahid M, Manjula BP, Sunil BV. A comparative study of intravenous paracetamol and intravenous tramadol for postoperative analgesia in laparotomies. Anesth Essays Res. 2015;9:314-9.
10. Semih Arici et al. Preemptive analgesic effects of intravenous paracetamol in total abdominal hysterectomy. AGRI. 2009;21(2):54-61.
11. Nikoda VV, Makarova VV, Maiachkin RB, Bondarenko AV. Clinical aspects of analgesia with intravenous paracetamol in the early postoperative period. Anesteziol Reanimatol. 2006;6:54-8.
12. Sinatra RS, Jahr JS, Reynolds LW, Viscusi ER. Efficacy and safety of single and repeated administration of 1 gram intravenous paracetamol injection for pain management after major orthopedic surgery. Anesthesiology. 2005;102(4):822–31.
13. Aghamir SK, Mojtahedzadeh M, Alizadeh F, Alizadeh F, Khalili H, Najafi A, et al. Propacetamol Vs. tramadol for post-operative pain management after urologic surgery. Internet J Pharmacol. 2005;4:2.
14. Uysal HY, Takmaz SA, Yaman F, Baltaci B, Basar H. The efficacy of intravenous paracetamol

versus tramadol for postoperative analgesia after adenotonsillectomy in children. J ClinAnesth. 2011; 23:53-7.

15. Turhan Togrul et al. Comparison of intravenous Paracetamol and Tramadol for postoperative analgesia in patients with septo-rhinoplasty. Journal of Anesthesia. 2011;19(4):213–16.
16. Howard S. Smith. Perioperative Intravenous Acetaminophen and NSAIDs. Pain Medicine 2011; 12:961–81.
17. Cade L, Ashley J. Prophylactic paracetamol for analgesia after vaginal termination of pregnancy. Anaesth Intensive Care. 1993;21:93–96.
18. Hein A, Jakobsson J, Ryberg G. Paracetamol 1 g given rectally at the end of minor gynecological surgery is not efficacious in reducing postoperative pain. Acta Anaesthesiol Scand 1999;43:248–51.
19. Kela M, Umbarkar S, Sarkar M, Garasia M. Comparative study of efficacy of IV paracetamol Vs IV tramadol for postoperative pain relief after cardiac surgery. Bombay Hosp J. 2011;53:582-6.
20. Cakan T, Inan Nurten et al. Intravenous paracetamol improves the quality of postoperative analgesia but does not decrease narcotic requirement. Journal of neurosurgical anesthiology. 2008 July;20(3):169-173.

Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(1) (Part - II): 263-267
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.37

Comparative Evaluation of Intravenous Granisetron Hydrochloride and Intravenous Lignocaine Hydrochloride to Alleviate the Pain on Propofol Injection

Jenish C Patel[1], Jayshree M Thakkar[2], Damini Makawana[3], Sanobar Khokhar[4], Saeed Vora[5], B C Shah[6]

[1]Junior Lecturer [2]Associate Professor [3]Associate Professor [4]1st Year Resident [5]Ex Resident [6]Professor, Department of Anaesthesia, Gujarat Cancer and Research Institute, Ahmedabad, Gujarat 380016, India.

Abstract

Propofol is one of the most commonly used induction agent. Pain on injection still remains a considerable concern for anaesthesiologist. The aim of the study was to assess the efficacy of granisetron HCL and ligocaine HCL to alleviate the pain on propofol injection. *Methods:* Fifty patients aged 18-50 years, ASA grade 1-2, posted for elective surgeries under general anaesthesia were randomly divided into two groups. Group G received 2 ml (1 mg/ml) granisetron while group X received 2 ml (2%) ligocaine intravenously before propofol injection. Manual venous occlusion was done for 1 minute after pre-treatment drug. 2 ml of total calculated dose of propofol was given over a period of 4 seconds. Patients were asked about the pain on injection with use of verbal rating score chart after 15 seconds. HR, SBP, DBP, SpO_2 was measured 0, 1, 3 minute after propofol injection. *Results:* HR, SBP and DBP were significantly raised in granisetron group as compared to lidocaine group. Average pain score in group G was 2.1 while in group X it was only 0.8, which was statistically significant. ($p<0.05$). *Conclusion:* We conclude that lignocaine HCL is better than granisetron for alleviating pain after propofol induction.

Keywords: Pain; Propofol; Lignocaine Hcl; Granisetron Hcl.

How to cite this article:

Jenish C Patel, Jayshree M Thakkar, Damini Makawana et al. Comparative Evaluation of Intravenous Granisetron Hydrochloride and Intravenous Lignocaine Hydrochloride to Alleviate the Pain on Propofol Injection. Indian J Anesth Analg. 2019;6(1):263-267.

Introduction

Pain is a vital function of the nervous system which warns the body of potential or actual tissue damage. The pain pathway begins with the specialized pain receptors (nociceptors) which are spread throughout the body. These nociceptors are stimulated by a number of stimuli like mechanical forces, thermal injuries as well as chemical substances. The noxious stimuli are converted into electrical stimuli and transported to spinal dorsal horn via A and C fibres. In the spinal cord these stimuli are carried via spinothalamic tracts into the thalamus and from there into the cerebral cortex. There are other accessory ascending & descending tracts which modulate the degree of

Corresponding Author: Jayshree M Thakkar, Associate Professor, Department of Anaesthesia, Gujarat Cancer and Research Institute, Ahmedabad, Gujarat 380016, India.

E-mail: drjmthakkar@yahoo.com

Received on 23.10.2018, **Accepted on** 14.11.2018

pain perception. Moreover, tissue damage causes release of PGs, TX, Serotonin and other chemical mediators which further sensitize the nociceptors and reduce the threshold of pain sensitivity.

Propofol (2, 6, di-isopropyl phenol) is a chemically phenol base anesthetic agent. Pain during injection of propofol is a very unpleasant and irritating event. Incidence of pain during propofol injection varies between less than 10% in large veins at the cubital fossa to 90% in veins at the dorsum of hand [1]. The immediate vascular pain on injecting propofol is attributed to the direct irritant effect of propofol on nociceptors at the intimal layer of vessel.

The delayed pain (after 10-20 sec) is probably due to activation of Kallikrien- Kinin system. Many factors affect the incidence of pain on injection like age of patient, site and size of veins, temperature, PH of the formulation, speed of injection, concentration in the aqueous phase and the buffering effect of blood.

Lignocaine is an amide based local anaesthetic [2] which blocks the Na^+ channel in the nociceptors and prevents the transmission of the noxious stimulus from nociceptor to the pain fibres. Moreover, as it is a weak base, it releases H^+ ion on contact with a lipid like propofol and thus decreases PH. Thereby decreasing concentration of free propofol molecules. These two mechanisms help to decrease pain at propofol injection.

Granisetron is a 5-HT3 receptor antagonist [3]. It blocks the effect of serotonin on the nociceptors and thus reduces the intensity of pain on propofol injection.

Other agents used to reduce pain of propofol includes Opioids [4], Ketamine [5], NSAIDS [6], Nitrous oxide [7], Steroids [8], ondansetron [9], thiopental sodium [10], $MgSO_4$ [11], NTG [11] etc. Ondansetron exhibits property of local anaesthetic. So, granisetron is also 5-HT3 receptor antagonist and may be exhibits local anaesthetic properties [12].

Aim of our study was to evaluate the comparison of granisetron and preservative free lignocaine in alleviating the pain of propofol after intravenous injection.

Material and Methods

After approval from institutional ethical committee, fifty patients aged between 18-50 years of age, of both sexes, belonging to ASA grade I & II, who were scheduled to undergo elective surgeries under general anaesthesia were randomly divided into two groups.

Informed consent from all patients were taken and explained about the procedure. Patients with history of allergy to lignocaine, propofol or granisetron were excluded. Patients belonging to ASA grade III, IV, those undergoing emergency surgery and those who could not communicate properly were also excluded.

Routine preanaesthetic evaluation was performed. All routine investigation was done. On arrival in the operating room, the baseline readings of HR, NIBP, SpO_2 and ECG of all patients were recorded. 20 G IV Cannula was inserted into a vein on the dorsum of patient's non-dominant hand & RL infusion started.

Verbal rating score was recorded during propofol injection.

Patients in Group G received 2 ml of (1 mg/ml) granisetron, while in Group X 2 ml 2% lignocaine were given over 5 seconds. Both drugs were given 5 min after IV cannulation.

At the time of propofol injection, manual occlusion at midarm was applied for 1 min and then released. Next propofol injection of 2 ml bolus was given over 4 second. 15 seconds after this small bolus dose, patients were asked to rate any pain sensation during the injection.

An anesthesiologist blinded to the study recorded the pain using the verbal rate scale:

0 = None (Negative response to questioning)

1 = Mild Pain (Pain reported only on questioning and no behavioural signs)

2 = Moderate Pain (Pain reported on asking with behavioural signs or pain reported spontaneously)

3= Severe Pain (Strong vocal response with facial grimacing, arm withdrawal or tears from eyes.)

After recording this, patients were induced with Glycopyrrolate 4 mcg/kg, Fentanyl 2 mcg/kg, Propofol 2.5 mg/kg and Succinyl choline 2 mg/kg IV. After IPPV with 100% O_2 tracheal intubation was done with appropriate sized portex endotracheal tube.

HR, NIBP, SpO_2 and ECG were recorded before propofol injection and at 0, 1 & 3 min after propofol.

Maintenance was done with N_2O, O_2, and vecuronium bromide 0.1 mg/kg IV and Isoflurane as volatile anaesthetic agent. At the end of surgery patients were reversed with neostigmine bromide 0.05 mg/kg and glycopyrrolate 5 mcg/kg IV and shifted to ICU.

Statistical analysis: Group X and Group G study results were statistically analysed by using unpaired

students 'T' test on graph pad software. P value < 0.05 was considered as statistically significant.

Results

All data were recorded and expressed in terms of mean±standard deviation. p value < 0.05 was considered significant. Statistical software from www.Graphpad/instate3 site was used.

Tables 1 shows both groups were comparable with respect to age distribution and gender and statistically not significant (p> 0.05).

Table 2 shows a different trend in both groups. The average HR at 0, 1 & 3 min after propofol injection were 79.6±7.73, 78.16±5. 83 and 76.76±5.88 in the lignocaine group while they were 80.4±9.06, 90.76±9.14 and 92.8±8.18 in the granisetron group was statistically significant (p < 0.0001) and was due to pain induced tachycardia.

Table 3 shows that the systolic blood pressure (SBP) at 0,1 & 3 minute after propofol injection were 122.9±9.88, 118.6±10.01 and 115.0±9.4 mm of Hg in the lignocaine group, while in the granisetron group, it was 126.4±9.87, 132.4±10.9 & 134.2±11.79 mm of Hg. The rise in SBP was more in the granisetron group and the difference in both groups was statistically significant (p < 0.0001).

Table 4 shows the diastolic blood pressure (DBP) in lignocaine group at 0, 1& 3 min were 72.7±7.09, 68.72±6.47 & 66.24±5.54 mm of Hg while DBP in granisetron group were 75.12±6.95, 79.04±8.64 and 82.0±8.92 mm of Hg. The DBP was significantly lower (p< 0.0001) in lignocaine group which shows better control of propofol pain during injection.

Table 5 shows the pain score (VRS) at 15 second. After propofol bolus (2 ml/4s) injection. The pain score in lignocaine group is 0.8±0.81 while in granisetron group it is 2.1±0.68. Now this is statistically significant (p < 0.0001). This means that lignocaine was more effective in blunting pain of propofol injection as compared to granisetron.

Hence the incidence of moderate to severe pain was quite high in granisetron group compared to the lignocaine group (p < 0.0001).

Table 1: Demographic Data

	Age (Yrs.)	p value	Sex (M:F)
Group G	42.5(3.5355)	1.0000	23:02
Group X	40.0(4.2426)	1.0000	18:07

All the data were represented as mean±SD.

Table 2: Changes of heart rate (bpm) at 0, 1, 3 min

Time	Group X	Group G	P value
O Min	79.60(±7.73)	80.40(±9.06)	0.7385
1 Min	78.16(±5.83)	90.76(±9.14)	0.0001(s)
3 Min	76.76(±5.88)	92.80(±8.18)	0.0001(s)

Table 3: Changes of SBP (mmHg) at 0, 1, 3 min

Time	Group X	Group G	P value
0 Min	122.96(±9.88)	126.48(±9.87)	0.2138
1Min	118.64(±10.01)	132.40(±10.96)	0.0001(s)
3 Min	115.04(±9.40)	134.24(±11.7)	0.0001(s)

Table 4: Changes of DBP (mmHg) at 0, 1, 3 min

Time	Group X	Group G	P value
0 Min	72.72(±7.09)	75.12(±6.95)	0.2329
1 Min	68.72(±6.47)	79.04(±8.64)	0.0001(s)
3 Min	66.24(±5.54)	82.00(±8.92)	0.0001(s)

Table 5: Pain score (VRS) at 15 sec

Time	Group X	Group G	P value
15 sec	0.8(0.81)	2.1(0.68)	0.0001(s)

Discussion

Nowadays anaesthesiologists are expected to provide their services with safe and uncomplicated technique to patient. The patient also expects painless, safe and uncomplicated anaesthesia for their operative procedures.

Propofol [13] (2-6-di isopropyl phenol) is one of the most popular anaesthetic induction agent for inducing general anaesthesia for surgery as well as for sedation in various procedures with many advantages and low incidence of side effects. The rapid action, smooth induction as well as quick recovery make it an ideal anaesthetic agent. But pain on injection limits its use, it is a common problem and can be very distressing to the patient.

Propofol preparation we use is a 1% (wt/vol) aqueous emulsion containing 10% w/v soybean oil, 2.25% glycerol and 1.2% purified egg phosphatide lecithin. The pH is 7 and pka of the drug in water is 11.

Scott RP et al. observed that the pain on injection is caused by activation of the Kallikrein-kinin system or by the lipid solvent in propofol by generating kinins, mainly bradykinin, local vasodilation & hyper permeability, increase the contact between the aqueous phase propofol and the free nerve ending. This pain has a delayed onset up to 10-20 seconds. They found that lignocaine mixed propofol was more effective than pre-

treatment with lignocaine in decreasing propofol injection pain. They found significant decrease in pain incidence from 46.7% to 13.5% by mixing lignocaine 10 mg with propofol as compare to pre-treatment with lignocaine 10 mg 30 second before propofol injection (46.7% to 40%) [14].

A 4 point verbal rate scale (VRS) was chosen in this study rather than visual analogue score (VAS). VAS required hand-eye coordination and it's not possible during the rapidly changing state of consciousness. So we used VRS in our study to quantity pain intensity. Dhananjay Kumar Singh et al. [11] and Ahmed et al. [17] also used 4 point verbal rate scale in their study.

Lignocaine is commonly used to decrease the pain on propofol injection [15,16,4]. Ondansteron has long been used for propofol pain by virtue of its mu opioid agonism, 5-HT_3 antagonism and Na^+channel blocking action [9]. We compared a novel drug granisetron which is a 5-HT_3 antagonist like ondansetron and expected to have some effects like it.

King Sy, Davis Fm, Wells JE et al. [2], in 1992 studied various dose of lignocaine and concluded that significant reduction in the pain from 73% with saline to 32% with 20 mg lidocaine 1 ml (1%).

G. Gehan et al. [15], studied optimal dose of lignocaine for preventing pain on propofol injection. They compared the different doses of lignocaine mix with with propofol 0.1 mg/kg, 0.2 mg/kg, 0.4 mg/kg and control group. They concluded that lignocaine 0.1 mg/kg significantly reduced the incidence of pain and there was no improvement as dose was increased. Haemodynamic changes were similar in all four groups and no significant cardiac event present due to lignocaine.

Agarwal et al. [10] in their study compared the efficacy of pre-treatment with thiopental 0.25 mg/ kg and 0.5 mg/kg and lignocaine 40 mg for prevention of propofol induced pain. They found 77% patients complained of pain in the group pre-treated with normal saline as compared with 39%, 37%, 3% in groups pre-treated with lignocaine 40 mg, thiopental 0.25 mg/kg and 0.5 mg/kg respectively. ($p<0.05$)

We also used 40 mg lignocaine and pain relief was in 40% of patients.

Sarita Fernandes et al. [18] also concluded that lidocaine is superior to acetaminophen in reducing the pain on injection of propofol.

Ahmed et al. [17] in 2012 in their study observed that pain reduced from 60% to 15% by pre-treatment with granisetron when the venous drainage was occluded manually at mid arm by assistant for 1 minute after IV injection.

We also used mid arm occlusion technique for our study.

Many other authors have compared lignocaine and granisetron with other drugs to relieving pain of propofol injection.

Ye JH, Mui WC, Ren J et al. [12] in 1997 studied that ondansteron exhibits the properties of a local anaesthetic. It acts as a Na^+ channel blocker, a 5 HT_3 receptor antagonist and mu opioid agonist.

Granisetron is a more 5HT_3 antagonist so relieved pain by a similar mechanism. We used granisetron 2 ml (1 mg/ml) for our study. Ahmed et al. [17], Swati et al. [19] and Dhananjay Kumar Singh [19] also used same dose of granisetron.

Swati et al. [19] also concluded that there was 100% no pain in granisetron group than saline group which was highly significant. While we compared granisetron and lignocaine and observed that lignocaine has good pain relief.

Dhananjay Kumar Singh et al. [11] studied that granisetron reduced the incidence of propofol injection pain most effectively than nitroglycerine followed by magnesium sulphate. They found that granisetron reduced the incidence of propofol injection pain to 40% from 88% in placebo at 15 seconds.

B P Manjula et al. [20] used lignocaine 30 mg and granisetron 2 mg as pre-treatment before propofol injection. They concluded that there was 76% in lignocaine group and 62% in granisetron group did not have pain, 12% and 20% had mild pain, 12% and 18% had moderate pain in lignocaine and granisetron group respectively.

R cork et al., studied in 2008 [21] a comparison of the verbal rating scale and the visual analogue scale for pain assessment. They found an excellent correlation between the two (Pearson coefficient $r = 0.906$ & $p < 0.001$)

The average heart rate (HR), SBP, DBP at 0, 1, 3 min after propofol injection were raised in granisetron group than lignocaine group. Ahmed et al. [17] also noticed that there was transient rise in HR in patients suffering from pain of VRS score 2-3 in both the groups but no changes in blood pressure. The haemodynamic data from this study are difficult to compare because of variation in study.

All studies showed that 5- HT3 antagonists (granisetron, ondansetron etc.) and local anaesthetic

(lignocaine) both reduced the pain of propofol injection.

In our study we use 2 ml (2%) lignocaine. Our study also showed good results with lignocaine in reducing the pain of propofol injection.

In our study the HR, SBP, DBP were significantly raised in granisetron group as compared to lignocaine group. Moreover in our study we found that average pain score with granisetron was 2.1 while with lignocaine it was 0.8 our results show that pre-treatment with lignocaine is more effective than pre-treatment with granisetron in relieving pain of propofol injection.

Conclusion

Propofol is very commonly used agent for induction of anaesthesia due to its smooth induction and excellent emergence. Pain on propofol injection is very common complaint which can be relieved by number of drugs. We conclude from our study that lignocaine hydrochloride is better than granisetron for alleviating pain of propofol injection.

References

1. Hye-Joo Kang, Mi-Young Kwon, Byoung-Moon Choi, Min-Seok Koo, Young-Jae Jang, and Myoung-Ae Lee. Clinical factors affecting the pain on injection of propofol. Korean J Anesthesiol. Mar 2010;58(3):239–43.
2. King SY, Davis FM, Wells JE, Murchinson DJ, Pryor PJ. Lidocaine for the prevention of pain due to injection of propofol. AnaesthAnalg. 1992;74:246-9.
3. Dubey PK, Sureshwar P. Pain on injection of propofol: The effect of granisetron. Clinical J. Pain 2003;19:121-4.
4. Nathanson MH, Gajraj NM, Russell JA. Prevention of pain on injection of propofol: A comparison of lidocaine with alfentanyl. AnesthAnalg. 1996;82:469-71.
5. C.H. Tan, MK Onsiong and S.W. Kua. The effect of ketamine pre-treatment and propofol injection pain in 100 women. Anaesthesia. 1998;53:296-07.
6. Nishiyama T. How to decrease pain at rapid injection of propofol: Effectiveness of flurbiprofen. J Anesth 2005;19:273-6.
7. Beh T, Splinter W Kim J. In children, nitrous oxide decreases pain on injection of propofol mixed with lidocaine. Canadian journal of Anesthesia. 2002 Dec;49(10):1061-3.
8. Singh M, Mohta M, Sethi AK, Tyagi A. Efficacy of dexamethasone pre-treatment for alleviating of propofol injection pain. European Journal Anesthesiology. 2005 Nov;22(11):888-90.
9. Ambesh SP, Dubey PK, Sinha PK. Ondansetron pre-treatment to alleviate pain on propofol injection: A randomised, controlled, double blind study. AnaesthAnalg. 1999;89:197-9.
10. Agarwal A, Ansari MF, Gupta D, Pandey R, Raza M, Singh PK, et al. Pre-treatment with thiopental for prevention of pain associated with propofol injection. AnaesthAnalg. 2004;98:683-6.
11. Dhananjay Kumar Singh, Parul Jindal, Gaurav Singh et al. Comparative study of attenuation of the pain caused by propofol intravenous injection, by granisetron, magnesium sulphate and nitroglycerine. Saudi Journal of anasthesia. 2011;5(1):50-54.
12. Ye JH, Mui WC, Ren J, Hunt TE, Wu WH, Zbuzek VK. Ondansetron exhibits properties of a local anaesthetic. Anesth Analg. 1997 Nov;85(5):1116-21
13. Rutter DV, Morgan M, Lumley J et al, ICI 35 868 (Diprivan): A new intravenous induction agent. Anaesthesia. 1980;35:1188.
14. Scott RP, Sunders DA, Norman J. Propofol: Clinical strategies for preventing the pain on injection; Anaesthesia. 1988 Jun;43(6):492-4.
15. Gehan G, Karoubi P, Quinet F. Optimal dose of lignocaine for preventing pain on injection propofol. British Journal of Anesthesia. 1991;66:324-6.
16. Cameron E, Johnston G, Crofts S, Morton NS. The minimum effective dose of lignocaine to prevent injection pain due to propofol in children. Anesthesia. 1992;47:604-6.
17. Ahmed A, Sengupta S, Das T, Rudra A, Iqbal A. Pre-treatment with intravenous granisetron to alleviate pain on propofol injection: A double blind, randomised, controlled trial. Indian J Anaesth. 2012;56:135-8.
18. Sarita Fernandes, Charusheela Thombre. Prevention of propofol injection induced pain: A comparison of acetaminophen with lidocaine. Scholars Journal of Applied Medical sciences (SJAMS) 2016;4(5B):1544-48.
19. Swati Bhatt, Bipin Kumar P and M R Upadhyay. Granisetron - A novel drug for pain alleviation in propofol injection. World journal of pharmacy and pharmaceutical sciences (WJPPS). 2015;4(07):1686-1701.
20. BP Manjula, Balachandra SR. A clinical study to compare the efficacy of pre-treatment with granisetron and lignocaine to alleviate pain on propofol injection. Indian journal of Science and Research (IJSR). 2016 Jan;5(1):1267-71.
21. R CORK et al. A comparison of the verbal rating scale and the visual analog scale for pain assessment. The journal of Anesthesiology. 2003;8(1):1-3.

Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; (Part - II) 6(1): 269-276
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.38

Prediction of Difficult Intubation in Apparently Normal Patients by Combining Modified Mallampatti Test and Thyromental Distance

Kiran Nelamangala[1], Ravi Madhusudhana[2], Dinesh Krishnamurthy[3]

[1]Associate Professor [2]Professor [3]Professor & Head, Dept. of Anaesthesiology, Sri Devaraj Urs Medical College, RL, Jalappa Hospital, SDUAHER, Tamaka, Kolar, Karnataka 563101, India.

Abstract

Context: Difficult intubation is associated with serious complications, more so when there is failure of intubation. Inability to secure the airway during general anaesthesia remains one of the leading causes of morbidity and mortality worldwide. The principle goal of this study was to find the best predicting test in patients who are apparently normal by a combination of Modified Mallampatti test and Thyromental distance and comparing it with Cormack and Lehane Score. *Aims:* To use Mallampatti test & Thyromental distance test during pre-operative assessment to determine incidence of difficult laryngoscopy and intubation; To combine sensitivity and specificity of both the tests and determine, if the combination of both the tests increases the predictability of difficult intubation. *Settings and Design:* Prospective clinical study. *Methods and Material:* The preoperative airway assessment of Mallampatti grading & thyromental distance was done on 300 ASA grade 1 & 2 patients, aged between 18-60 yrs presenting for surgeries under general anesthesia. The preoperative Mallampatti test grading and the thyromental distance was compared with Cormack & Lehanelaryngoscopic grade. *Statistical analysis used:* Data was entered in to Microsoft Excel Worksheet and analyzed using SPSS (ver. 18) statistical package. In addition to sensitivity and specificity, the positive and negative predictive values were calculated. *Results:* The Mallampatti grade 3 & 4 were considered as predictors of difficult intubation 28 cases out of 300 patients (9.3%) of the study population belong to this group. Thyromental distance < 6 cm was considered as predictor of difficult intubation There were 17 cases out of 300 patients (5.7%) belonging to this group. When a combination of Mallampatti test and thyromental distance was used as a predictor of difficult intubation, there were 16 patients, which constituted 5.3% of the total cases. The incidence of difficult intubation is found to be 5%. *Conclusions:* The above result shows that the discriminative power is greater in combination of test than when used alone.

Keywords: Difficult Intubation; Mallampatti Test; Thyromental Distance.

How to cite this article:

Kiran Nelamangala, Ravi Madhusudhana, Dinesh Krishnamurthy. Prediction of Difficult Intubation in Apparently Normal Patients by Combining Modified Mallampatti Test and Thyromental Distance. Indian J Anesth Analg. 2019;6(1):269-276.

Introduction

An anaesthesiologist's fundamental responsibility is intubation and maintenance of patients airway which is the important step in anaesthesia practice. Difficult intubation is associated with serious complications, more so when there is failure of intubation. Inability to secure the airway during general anaesthesia remains one of the leading causes of morbidity and mortality worldwide. It is the responsibility of the anesthesiologist to perform an evaluation in order to predict potential difficult intubation. The principle goal of this study was to find the

Corresponding Author: Ravi Madhusudhana, Professor, Dept of Anaesthesiology, Sri DevarajUrs Medical College, RL, Jalappa Hospital, SDUAHER, Tamaka, Kolar, Karnataka 563101, India.

E-mail: ravijaggu@gmail.com

Received on 05.11.2018, **Accepted on** 03.12.2018

best predicting test in patients who are apparently normal by a combination of Modified Mallampatti test and Thyromental distance and comparing it with Cormack and Lehane Score.

The American society of Anesthesiologists (ASA) has defined endotrachel intubation as when proper placement of endotracheal tube with conventional laryngoscopy requires more than three attempts or more than 10 minutes. Difficult airway is also defined as a clinical situation in which conventionally trained anaethesiologist experiences difficulty with mask ventilation or difficult tracheal intubation or both [1]. Difficult intubation is the second most frequent proclaimed damaging event leading to anesthesia malpractice claims [2].

The ASA database of adverse respiratory events has found that a vast majority (85%) of airway related events involves brain damage or death, and as many as 1/3rd of death is attributed solely to anesthesia due to inability to maintain patent airway [3].

Occasionally with a patient who has difficult airway, the anesthesiologist is faced with a situation where mask ventilation is proved difficult or impossible. This is the most critical emergency that might be faced in the practice of anesthesia [4]. Most catastrophes have occurred when possible difficult airway was not recognized [5].

When anatomical abnormalities are hidden in the air passage, it is likely to be missed. In such patients if difficult intubation is predicted, it may be helpful. During routine anesthesia, the incidence of difficult intubation has been estimated at 5.8% [6].

Although an array of tests are available to predict difficult intubation, it is difficult to for the anesthesiologist as, no single score or combination of scores can be trusted to detect all patients who are difficult to intubate [7]. No system has yet been devised that has 100% positive predictive value or 100% sensitivity and specificity [8]. Hence unidentified difficult intubation can be challenging to the anesthesiologist.

The various bedside screening tests available to predict difficult intubation are the Mallampatti test which was introduced by Mallampatti S Rao and co-workers in 1985, which is classified based on visibility of oropharyngeal structures [9].

The distance from thyroid notch to mentum (thyromental distance), the distance from upper border of manubrium sterni to mentum (sternomental distance) and simple summation of risk factors (Wilson's risk score) are widely recognized as tools for difficult intubation [10,11].

Nevertheless the diagnostic accuracy of these screening tests has varied from trial to trial probably because of difference in the incidence of difficult intubation, inadequate statistical power, different test thresholds, or difference in patient characteristics. Question remains as to whether a combination of tests may improve predictive accuracy.

Therefore there is a need for a test that is quick and easy to perform at the bedside that is sensitive so that majority of difficult cases can be identified and is also highly specific.

Aims and Objectives

To use Mallampatti test during pre–operative assessment to determine incidence of difficult laryngoscopy and intubation; to use Thyromental distance test during pre-operative assessment to determine incidence of difficult laryngoscopy and intubation; to combine sensitivity and specificity of both the tests and determine, if the combination of both the tests increases the predictability of difficult intubations.

Materials and Methods

Source of data

300 consecutive (apparently normal) American Society of Anesthesiologist grade 1 & 2 adult patients undergoing elective surgical procedures under general anesthesia with endotracheal intubation at a tertiary care hospital,were the subjects in this study. Study design was Prospective clinical study.

Inclusion Criteria

All patients aged between 20 to 60 years of either sex; patients belonging to ASA (American Society of Anesthesiologist) Grade 1 and 2 Physical status; patients undergoing elective surgery under general anesthesia with endotracheal intubation.

Exclusion Criteria

Pregnant patients; patients with body mass index more than 30; mouth opening less than 3 cms; mid-line neck swellings; difficult neck movements; ASA (American Society of Anesthesiologists) 3 and 4 patients.

Methodology

Preanesthestic evaluation: The preanesthestic evaluation of patient was done in the ward. The consent was taken for surgical procedure, anesthetic technique and study. Evaluation of the patient was done by history of medical illnesses, surgical procedure, medication, drug allergy and general physical examination. Blood pressure, pulse, hydration were noted, body mass index was calculated, systemic examination was done and American Society of Anesthesiologist (ASA) grading was determined.

Airway Assessment: Airway was assessed by modified Mallampatti test and thyromental distance.

Modified Mallampatti Test: It is done by examiner sitting in front of the patient, who should be sitting up with head in neutral position and the patient is asked to open their mouth maximally and protrude the tongue without phonating and Mallampatti grading is done accordingly.

Grade 1: Visualization of soft palate, fauces, uvula, anterior and posterior pillars.

Grade 2: Visualization of soft palate, fauces and uvula.

Grade 3: Visualization of soft palate and base of uvula.

Grade 4: Only Hard palate is visible, soft palate is not visible at all.

Grades 3 and 4 are classified as predictor of difficult intubations.

Assessment of airway using Thyromental distance:

Done using a measuring tape from the mentum of the mandible to thyroid notch in the midline with neck in full extension. Measurement of less than 6 cms is considered to be predictor of difficult intubation.

Patient Preparation

All patients were premedicated with Tab. Ranitidine 150 mg and Tab. Diazepam 10 mg given orally night before surgery.

On the morning of surgery patient were shifted to the O.T, Non-Invasive Blood pressure, ECG, SpO2 monitors were connected and basal vitals were recorded. Patients were given Inj Pentazoscine 20-30 mg, Inj Midazolam 25 µg/kg given IV and pre oxygenated for 3 mins with 100% Oxygen.

Induction done with sleep dose of Thiopentone (approx 5 mg/kg) IV and relaxation done with inj Vecuronium 0.1 mg/kg IV. Patients were ventilated with 50% Nitrous oxide and 1% Halothane in oxygen. After 3 mins laryngoscopy was done in sniffing position by using Macintosh blade no 3/4. Cormack & Lehane grading was done accordingly by a senior anesthesiologist with more than two years experience post qualification. Subsequently the patients were intubated.

The following is the Cormack and Lehane grading:

Grade 1: Visualization of entire laryngeal aperture.

Grade 2: Visualization of only posterior commissure of laryngeal aperture.

Grade 3: Visualization of only epiglottis.

Grade 4: Visualization of only soft palate.

Grade 3 and 4 predict difficult intubation. The patients were intubated with appropriate sized endotracheal tube which were secured and anesthesia was maintained.

Results

Three hundred apparently normal ASA grade 1 & 2 adult patients in the age group 18-60 yrs of either sex posted for elective surgical procedures were prospectively studied.

Method of Statistical Analysis

The following methods of statistical analysis have been used in this study. The data were entered into a Microsoft Excel Worksheet and analyzed using SPSS (ver. 18) statistical package.

The results were presented in number and percentage in tables and figures.

The sensitivity and specificity of Mallampatti Grade predictor, Thyromental distance Predictor and Mallampatti + Thyromental distance, compared to the Cormack and Lehane Grading were determined. In addition to sensitivity and specificity, the positive and negative predictive values were calculated.

In our study Average age noted was 37.14±14.14; BMI was 24.04±1.687; female patients were 172 and male 128; Mallampatti grade 3 and 4 were considered as predictors of difficult intubation.28 cases out of 300 patients (9.3%) belonged to Mallampatti grade 3 and 4, remaining 272 were Mallampatti grade 1 & 2. Thyromental Distance

was found to be less than 6 cm in 17 and more than 6 cm in 283 patients. The Mallampatti Grade and Thyromental Distance in the Study Population as a combination was positive in 16 patients and negative in 284 patients.

Table 1: Distribution and Correlation of Mallampatti Grade with Cormack & Lehane Grade in prediction of difficult Intubation

Cormack and Lehane Grading	Mallampatti Grade predictor +ve (grade 3&4)	-ve(grade 1&2)	Total
+Ve (grade 3&4)	19	3	22
	86.4%	13.6%	100.0%
	67.86%	1.11%	7.33%
-Ve (grade 1&2)	9	269	278
	3.2%	96.8%	100.0%
	32.14%	98.89%	92.67%
Total	28	272	300
	9.3%	90.7%	100.0%
	100.0%	100.0%	100.0%

Table 2: Distribution and Correlation of Thyromental Distance with Cormack & Lehane Grade in prediction of difficult Intubation

Cormack & Lehane Grading	Thyromental Distance < 6 Cm	> 6 Cm	Total
+Ve (grade 3&4)	12	10	22
	54.5%	45.5%	100.0%
	70.59%	5.53%	7.33%
-Ve (grade 1&2)	5	273	278
	1.8%	98.2%	100.0%
	29.41%	96.46%	92.67%
Total	17	283	300
5.7%	94.3%	100.0%	
100.0%	100.0%	100.0%	

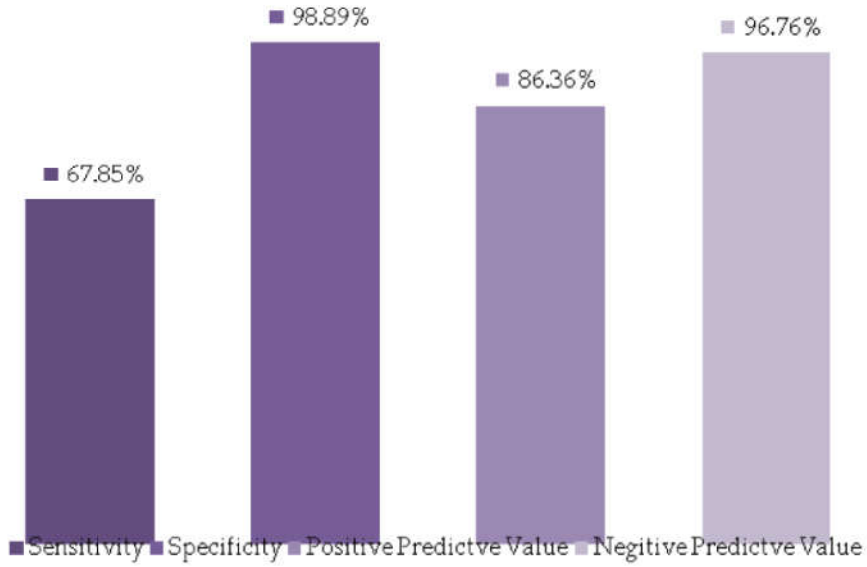


Fig 1: Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value of Cormack & Lehane Grading Vs Mallampatti Grade Predictor

The incidence of difficult intubation is found to be 5%

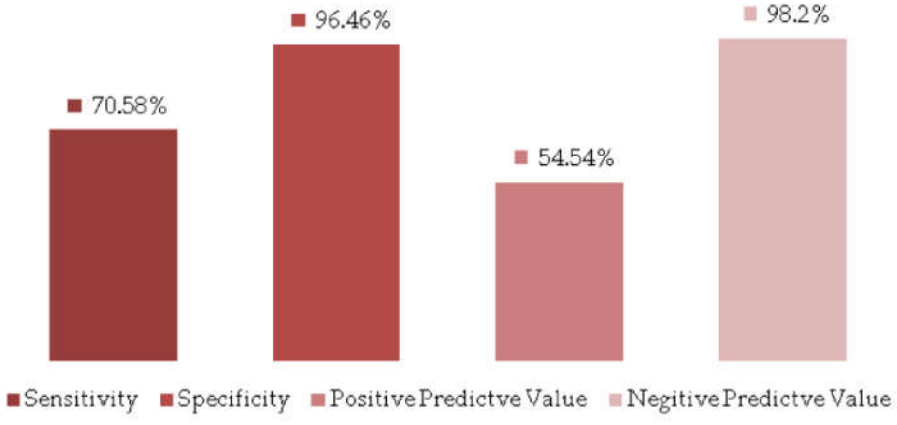


Fig 2: Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value of Cormack & Lehane Grading Vs Thyromental Distance Predictor

Table 3: Distribution and Correlation by Combination of Tests: The Mallampatti Grade and Thyromental distance with Cormack & Lehane grade in Prediction of difficult Intubation

Cormack and Lehane Grading	Mallampatti Grade		Total
	+ve(grade 3 &4)	-ve(grade 1 &2)	
+Ve	12	3	15
	80%	20%	100%
	75%	1.1%	5%
-Ve	4	281	285
	1.4%	98.6%	100%
	25%	98.9%	95%
Total	16	284	300
	5.3%	94.7%	100.0%
	100.0%	100.0%	100.0%

Table 4: Distribution of Combination of Tests - The Mallampatti Grade and Thyromental distance in Various Age Groups

Age	Mallampatti+Thyromental distance		Total
	+Ve	-Ve	
21 – 30 Yrs	5	108	113
	4.4%	95.6%	100.0%
31 – 40 Yrs	3	56	59
	5.1%	94.9%	100.0%
41 – 50 Yrs	1	52	53
	1.9%	98.1%	100.0%
51 – 60 Yrs	8	58	66
	12.1%	87.9%	100.0%
Total	17	283	300
	5.7%	94.3%	100.0%

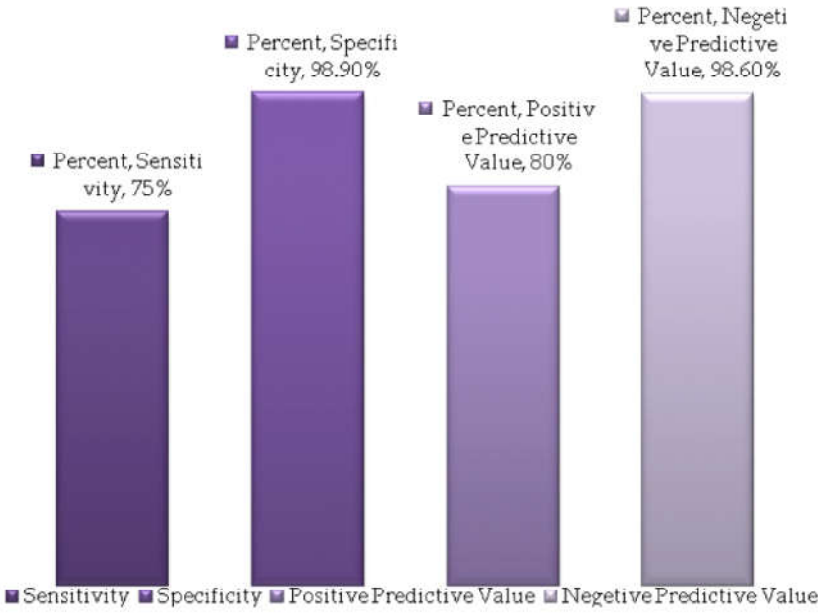


Fig 3: Sensitivity, specificity, PPV and NPV of Cormack and Lehane grading **vs**Mallampatti + Thyromental distance

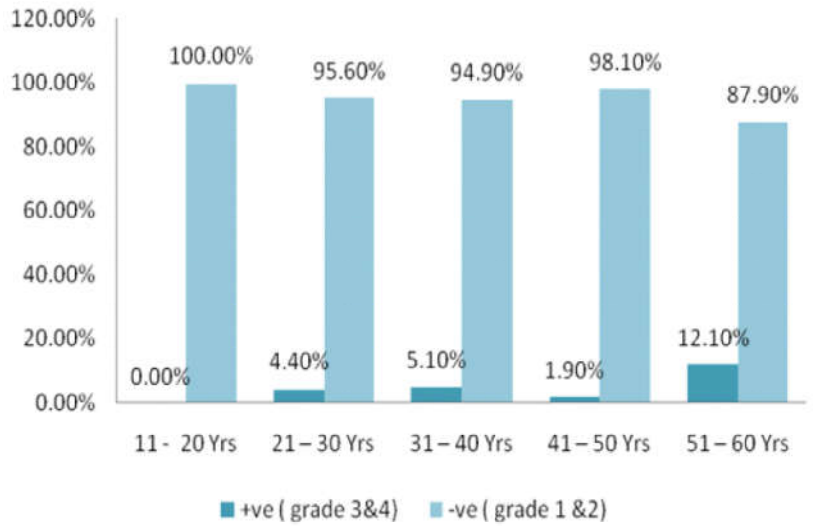


Fig 4: Distribution of combination of tests in various age groups

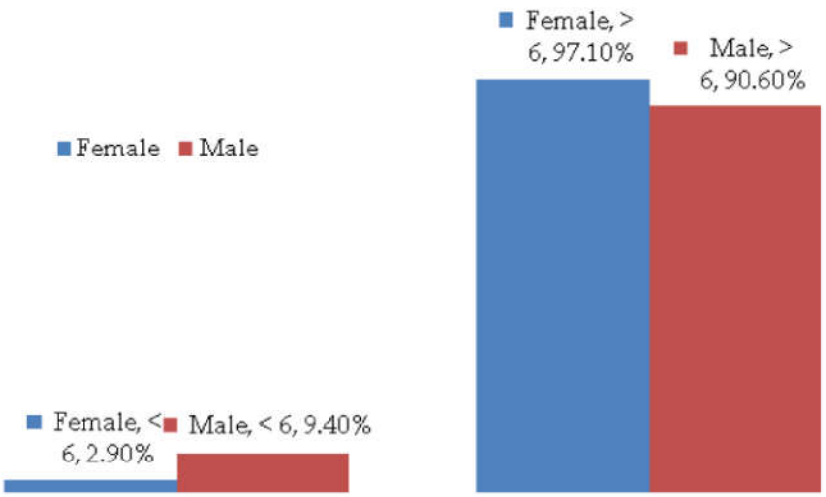


Fig 5: Gender and The Mallampatti Grade and Thyromental distance distribution of study population

Table 5: Distribution of Combination of tests The Mallampatti Grade and Thyromental distance in Male & Female

Gender	Mallampatti Grade + Thyromental distance		Total
	+Ve	-Ve	
Female	5	167	172
	2.9%	97.1%	100.0%
	29.40%	59.01%	57.3%
Male	12	116	128
	9.4%	90.6%	100.0%
	70.60%	40.99%	42.7%
Total	17	283	300
	5.7%	94.3%	100.0%
	100.0%	100.0%	100.0%

Discussion

In earlier days anesthesia was induced by anesthetic vapours given through face mask. Due to inability to maintain a patent airway, adequate depth of anesthesia for surgical procedures and its complication leading to morbidity and mortality led to development of safer anesthetic practice by maintaining anesthesia through endotracheal insufflation.

The endotracheal tube is one of the airway devices which can be introduced into the trachea either orally or nasally, to maintain a patent airway in both unconscious and Anaesthetized patients. The significance of difficult or failed tracheal intubation following induction is a well recognized cause of morbidity and mortality in anesthetic practice. Moreover the need to predict potentially difficult tracheal intubation has received wide attention but withmeagre success.

Many anatomical characteristics and pathological conditions (like Pierre Robin syndrome, Ludwig's angina) have been suggested to be useful in assessing anticipated difficult intubation by altering or distorting the regional anatomy of the airway Unheralded difficult intubation is a risk to the patient's life and a challenge to the skill of the anesthesiologist.

In the absence of pathological conditions, radiographic methods are time consuming and cannot be used routinely for prediction of the difficult intubation. But these factors have limitations because of observer variability, inadequate statistical power and difference in incidence of difficult intubation Based on these observations and studies, our study was conducted to overcome a few of these limitations and hence we have used two simple bed side airway assessment tests i.e., Mallampatti test and measurement of thyromental distance to predict the incidence of difficult intubation.

The study population consisted of 300 ASA grade 1 & 2 patients with apparently normal airway who underwent surgical procedures under general anesthesia. In our study the prediction of difficult intubation was done by combining Mallampatti test grade 3 & 4 and thyromental distance < 6 cm during the preoperative airway assessment and correlating it with the Cormack & Lehane laryngoscopic grading at intubation. Grade 3 & 4 of Cormack & Lehane was considered difficult intubation.

Butler PJ. et al. conducted on 250 patients, who did the pre-operative airway assessment by Mallampatti test and thyromental distance [12].

The incidence of difficult laryngoscopy in their study was 8.2%. Yildiz TS et al. conducted study on 1674 patients of ASA 1-3, whose pre-operative airway assessment was done with Mallampatti and Thyromental distance. They found incidence of difficult intubation was 4.8% and increased with age [13].

Ittichaikuthol W et al. conducted study on 1888 patients undergoing elective surgery under general anesthesia. Airway was evaluated using Mallampatti test and Thyromental distance. They found incidence of difficult intubation to be 3.2% [14].

Khan ZH et al. conducted a prospective study on 380 patients for assessment of airway using various screening tests including Mallampatti test and Thyromental distance. The prevalence of difficult intubation was 5% [15].

Shiga et al. conducted a meta-analysis of bed side screening tests for difficult intubation in apparently normal patients with no airway pathology. Tests included Mallampatti test, Thyromental distance, Sternomental distance and Wilson score. They found an overall incidence of difficult intubation to be 5.8% [16]. The incidence of difficult intubation in our study is 5%, which is comparable to the above mentioned study.

Similar study conducted by Koh et al. on 605 patients, a combined Mallampatti test grade 3 & 4 and thyromental distance < 6 cm was noted during preoperative airway assessment and correlated to Cormack & Lehane laryngoscopic grading during intubation. Grade 3 & 4 were considered difficult intubation [17].

Vani et al. conducted a study on 50 patients whose preoperative airway assessment combined Mallampatti grade 3 & 4 and thyromental distance < 6 cm to Cormack & Lehane grading during intubation. Grade 3 & 4 were considered difficult intubation [18].

Study conducted by Ezri et al. on 1472 patients also used similar parameters for prediction of difficulty during intubation. The results obtained in our study in predicting difficult airway using Mallampatti test alone was found to be having a sensitivity of 67.85% and specificity of 98.89%, the positive predictive value was 86.36%, and a negative predictive value was 96.76% [19].

Iohom et al. conducted a study in predicting difficult airway by using Mallampatti test, thyromental distance and sternomental distance. They found the sensitivity of Mallampatti test to be 43%, specificity 93%, the results of our study are comparable to the values obtained to this study [20].

In our study when thyromental distance was used alone in assessing the difficult airway, the sensitivity was 70.58%, specificity was 96.46%, positive predictive value was 54.4% and the negative predictive value was 98.2%. Frerk conducted a study in predicting difficult airway by using Mallampatti test and thyromental distance. The sensitivity of thyromental distance was found to be 88% and specificity 81% which are comparable to this study [21]. When the combination of Mallampatti test and thyromental distance was used to assess difficult airway and it was used to correlate it with Cormack and Lehanelaryngoscopic grading, the sensitivity was 75%, specificity 98.9%, positive predictive value 80% and negative predictive value 98.6% was obtained. The above result obtained show that, the discriminative power is greater when used in combination rather than alone.

Ulrich B et al. in 1998 conducted a study on 1993 patients surgical patients showed if during the laryngoscopy, a satisfactory laryngeal view is not obtained, the backward – upward-rightward-pressure (BURP) manoeuvre may aid in improving the view. The BURP manoeuvre has shown to improve the laryngeal view, decreasing the difficult intubation in these patients from 4.8% to 1.8% [22].

Benumof et al. described optimal external laryngeal manipulation by pressing posteriorly and cephalad over the thyroid, cricoid, and hyoid improved the laryngeal view by at least one Cormack & Lehane grade [23].

In our study the patients with difficult airway determined by Cormack and Lehane grade 3 & 4 were intubated either by "BURP" manoeuvre or bougie. There were 22 patients belonging to Cormack & Lehane grade 3 and 4 out of which 17 patients were intubated with BURP manoeuvre and 5 patients were intubated with bougie. The airway management was not associated with any patient morbidity or mortality. Further, surgery was never cancelled or postponed secondary to difficulties with airway management.

Conclusion

In our study the incidence of difficult intubation was found to be 5%. No single anatomical factors can be used as a sole predictor of difficult intubation, with few exceptions. Patients with obvious pathological and anatomical deformity of airway have difficult intubations. The present study has shown that the combination of modified Mallampatti test and thyromental distance is better than when used alone in predicting difficult intubation.

Conflict of Interest: None

References

1. Practice guidelines for management of the difficult airway. A report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Anesthesiology. Anesthesiology. 1993 Mar;78(3):597-602.
2. Miller CG. Management of the difficult intubation in closed malpractice claims: ASA news letter. 2000; 64:13-19.
3. Caplan RA, Posner KL, Ward RJ, Cheney FW. Adverse respiratory events in anesthesia: A closed claims analysis: Anesthesiology. 1990;72:828.
4. Largeron O, Masson E, Haraux C, Guggiari M, Biareli A, C oriat P, Riou B. Difficult tracheal intubation and mask ventilation. Anesthesia. 2000; 92:1229-35.
5. Benumof JL. Management of the difficult adult airway with special emphasis on awake tracheal intubation. Anesthesiology. 1991;75:1087-10.
6. Shiga Toshiya, Wajima Z, Inoue T, Sakamoto A. Predicting difficult intubation in apparently normal patients, A meta-analysis of bedside screening test performance. Anesthesiology. 2005;103:429-37.
7. Wilson, ME. Predicting difficult intubation. British Journal of Anaesthesia. 1993;71:333–4.
8. Gonzalez H; Minville V; Delanoue K; Mazerolles M; Concina D; Fourcade O. The importance of increased neck circumference to intubation difficulties in obese patients. Anesthesia and Analgesia. 2008;106:1132–6.
9. Mallampatti SR, Gatt SP, Gugino LD, Desai SP, Waraksa B, Freiberger D et al. A clinical sign to predict difficult tracheal intubation: a prospective study. Can Anaesthsoc j 1985;32:429-34.
10. Jansenns M, Harstein G; Management of difficult intubation; Eur J Anaesthesiol 2001;183-12.
11. Wilson ME, Spiegelhalter D, Robertson JA, Lesser P. Predicting difficult intubation. British journal of Anesthesia. 1988;61:211-6.
12. Butler PJ, Dhara SS. Prediction of difficult laryngoscopy; An assessment of the thyromental distance and Mallampatti predictive tests; Anaesth Intensive care. 1992;20:139-42.
13. Yildiz TS, Korkmaz F, Solak M, Toker K, Erciyes N, Bayrak F et al. Prediction of difficult intubation in Turkish patients. Eur J Anesthesiol. 2008;25:694-5.
14. IttichaikutholW,ChanpradubS,Amnoundetchakorn S, Arayajarernwong N, Wongkum W. Modified Mallampatti test and thyromental distance as a predictor of difficult laryngoscopy in Thai patients. J Med Asso Thai. 2010;93:84-9.
15. Khan Z H, Mohamaddi M, Rosouli M R, Farrokhnia F, Khan RH. Prediction of easy laryngoscopy and intubation." Anesth Analog. 2009;109:822-4.
16. Shiga T, Wazima Z, Inove T, Sakamoto A; Prediction of difficult intubation in apparently normal patients. Anesthesiology. 2005;103:429-37.
17. Koh LK, Kong CE, Ip-Yam PC; The modified Cormack & Lehane score for the grading of direct laryngoscopy; Evaluation in the Asian population. Anaesth Intensive care. 2002;30:48-51.
18. Vani V, Kamath SK, Naik LD, The palm print as a sensitive predictor of difficult laryngoscopy in diabetics; A comparison with other airway evaluation indices. J post grad Med. 2000;46:75-9.
19. Ezri T, Medalion B, Weisenberg M, Szmuk P, Warters RD, Charuzi I; Increased body mass index per se is not a predictor of difficult laryngoscopy; Canadian journal of Anesthesia. 2003;50:179-83.
20. Iohom G, Ronayne M, Cunningham AJ. Prediction of difficult tracheal intubation. Eur J Anaesthesiol. 2003;20:31-6.
21. Frerk CM. Prediction of difficult intubation. Anesthesia. 1991;46:1005-8.
22. Ulrich B, Listyo R, Gerig HJ, Gabi K, Kreienbühl G. The value of BURP and 3 predictive tests of difficult intubation .Anaesthestsist. 1998;47:45.
23. Benumof JL, Cooper SD. Quantative improvement in laryngoscopic view by optimal external laryngeal manipulation. J ClinAnaesth. 1996;8:136.

Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(1) (Part - II): 277-282
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.39

Comparative Study of two doses of Magnesium Sulfate as an Adjuvant in Supraclavicular Brachial Plexus block for Post Operative Analgesia

Nanda S Nandyal[1], Gajendra Singh[2], KSR Murthy[3]

[1]Assistant Professor [2]Associate Professor [3]Professor and Head, Department of Anaesthesia, Mahadevappa Rampure Medical College, Kalaburagi, Karnataka 585105, India.

Abstract

Aims and Objectives: To compare the duration of post operative analgesia with different doses of magnesium sulphate as an adjuvant in USG guided supraclavicular brachial plexus block and its side effects. *Material & methods:* Ninety patients aged 18-50 yr ASA Gr 1-2 divided into 3 groups of 30 each undergoing upper limb surgery under USG guided supraclavicular brachial plexus block. Group C (control group)- (n=30) received 20 ml of 0.5% Bupivacaine + 5 ml of normal saline (NS). Study group 1 (S1) - (n=30) received 20 ml of 0.5% Bupivacaine + 4 ml of NS + 100 mg (1ml) of magnesium sulfate. Study group 2 (S2) - (n=30) received 20 ml of 0.5% + Bupivacaine + 3 ml of NS & 2 ml (200 mg) of magnesium sulphate. *Results:* Onset of sensory block in Group S2 (6.5±1 min), in S1 (10±2.8 min) and in C (15±3 min). Onset of motor block in S2 (9±2 min), in S1 (13±2.2 min) and in C (19±2 min). Duration of post-operative analgesia in S2 (540±25 min), in S1 group, (440±20 min) and in control group C (200±15 min). Addition of $MgSO_4$ as adjuvant hastened the onset of sensory and motor block in study group as compared to control. Duration of sensory and motor block were more in group S2 as compared to S1 and C. Duration of postoperative analgesia was significantly prolonged in group S2 as compared to S1 and C ($p<0.001$) without increased incidence of side effects. *Conclusions:* Addition of magnesium sulphate to local anesthetics in brachial plexus block prolongs the duration of postoperative analgesia. It is dose related, 200mg has greater efficacy than 100mg without increased side effects.

Keywords: Magnesium Sulphate; Postoperative Analgesia; Brachial Plexus Block; Visual Analogue Scale.

How to cite this article:

Nanda S Nandyal, Gajendra Singh, KSR Murthy. Comparative Study of two doses of Magnesium Sulfate as an Adjuvant in Supraclavicular Brachial Plexus block for Post Operative Analgesia. Indian J Anesth Analg. 2019;6(1):277-282.

Introduction

Supraclavicular brachial plexus block is widely used for upper limb surgeries (forearm and hand). It is easy, safe with rapid onset and high success rate [1,2]. This block is performed at the level of brachial plexus trunk which blocks the majority of sensory, motor and sympathetic innervations.

USG guided technique allows to see subclavian artery as a prominent marker and neural structures around it above first rib [3] thus increasing success rate and reducing the complications of landmark technique.

Local anesthetics have shorter duration of action and needs additives to increase the duration of postoperative analgesia. Clonidine,

Corresponding Author: Gajendra Singh, Associate Professor, Department of Anaesthesia, Mahadevappa Rampure Medical College, Kalaburagi, Karnataka 585105, India.

E-mail: gajendra.glb@gmail.com

Received on 02.01.2019, **Accepted on** 07.01.2019

[4] buprinorphine, [5] tramadol, [6] were used in various studies for early onset and prolonged duration of analgesia providing excellent conditions for surgery. $MgSO_4$ also is an excellent additive to local anesthetics in regional and peripheral nerve blocks [7].

Mechanism of analgesic property of Magnesium on peripheral nerve is explained by surface charge theory [8], high concentration of divalent ions (Mg^{2+}) attracted by negative charges on the outer surface of nerve membrane causes effect on sodium channel gate which results in persistent hyperpolarisation and no conduction of impulse. Another mechanism is voltage dependant. Antagonism of NMDA receptor which prevents central sensitisation from peripheral stimulation and decreases the pain.

Different studies are conducted for $MgSO_4$ as additive to brachial plexus block with fair outcomes. This study was conducted to compare the efficacy of low dose and high dose of $MgSO_4$ for duration of postoperative analgesia and incidence of side effects.

Materials and Methods

Ethical committee approval was obtained and male and female patients of 18 to 50 years age, ASA Grade I or II, undergoing upper limb surgery under USG guided brachial plexus block, were divided into 3 groups of 30 each.

Group C: received 20 ml 0.5% bupivacaine+5 ml of NS

Group S_1: received 20 ml of 0.5% bupivacaine+ 4 ml of NS + 1 ml (100mg) magnesium sulphate.

Group S_2: received 20 ml of 0.5% bupivacaine + 3 ml of NS + 2 ml (200 mg) magnesium sulphate to total volume of 25ml and final concentration of bupivacaine 0.4% in each group.

For calculation of sample size, pilot study was done in 15 patients and randomized in 3 groups of 5 each. The standardized effective size 'cohen's 'd' was calculated, 23 patients per group were required to get stastically significant difference at p=0.05 and 80% power. By taking into consideration, block failure, exclusion, sample size was taken 30 in each group.

One sample Kalmogorov – smirnov test was used to determine differentiation between data sets from normal distribution.

Normally distributed data were analysed using analysis of variance. Catagorical data was analysed by chi square test.

Bonferroni correction was used to correct for multiple testing at different time points.

Study Method

Prospective double blind randomized controlled trial., Randomization done by computer generated random number table.

Exclusion Criteria

Contraindication to block (infection or bleeding disorders), history of cardiac disease, hepatic or renal failure, patients on long term calcium channel blockers, respiratory disorders, neuromuscular disorders, allergy to local anesthetics, mentally retarded patients, pregnant woman, neuropathy, ASA III and IV, failed block.

Thorough pre anesthetic evaluation was done, anesthesia procedure and Visual Analogue Scale (VAS) was explained to patients.

Written and informed consent was obtained. Patients were kept nil orally after 10 pm, oral antacids and anxiolytics were given.

In the operation theatre, monitoring devices were set up, IV line secured, Ringer Lactate infusion was started. Baseline parameters i.e. Heart Rate, Mean arterial pressure, oxygen saturation and respiratory rate were noted.

Procedure explained to patient and placed in supine position with head turned to opposite side. After cleaning and draping, local infiltration was done in supraclavicular area, block was performed by using high frequency linear probe, pulsatile subclavian artery was identified and confirmed with Doppler flow. Plexus located posterolateral to artery with hyper echoic honeycomb appearance. 23 gauge lumbar puncture needle is inserted by using in-plane technique and the drug is injected according to group allocation after negative aspiration for blood. Patient and observer were blind about the study solution. Vital parameters were monitored every 3 min for 30 min, and thereafter every 15 min till the end of surgery.

Sensory block is assessed by three point scale with pin prick method.

Grade 0 = sharp pin prick felt

Grade 1 = loss of pin prick sensation (analgesia) but dull sensation felt.

Grade 2 = loss of sensation (anesthesia)

Motor block is graded as

Grade 0 = normal motor function with full movement of wrist and fingers.

Grade 1 = decreased movements

Grade 2 = complete loss of movements (paralysis)

Assessment of sensory and motor blocks was done every 3 min till 30 min or till complete block is obtained. Assessment was done every hourly in intraoperative period for analgesia and every two hourly in postoperative till the requirement of systemic analgesics.

Onset of sensory block is defined as time interval between administration of drug and complete loss of sensation, and duration is time interval between drug injection and complete recovery of sensation to pin prick. Onset of motor block is defined as time interval between drug injection and complete loss of movement of fingers and duration is time interval between drug injection to complete recovery of finger movements and muscle power. Duration of surgery is time interval between skin incision to skin closure. Duration of analgesia is defined as time interval between drug injection and first injection of systemic analgesics.

Duration of analgesia or duration of sensory block is defined as the time from complete establishment of sensory block to the time of first rescue analgesia.

Analgesia was assessed by using 10 cm Visual Analogue Scale (VAS). Markings of 0 at the extreme left indicates no pain and 10 at the extreme right indicating maximum pain. Patients were asked to mark a point according to intensity of pain. When patient felt pain with VAS > 3, rescue analgesia was provided with either Inj. Diclofenac or Inj. Tramadol.

All patients were monitored in perioperative period for hemodynamic stability, any side effects of the block i.e. arterial puncture, pneumothorax, phrenic nerve palsy, failure of block or inadequate block and the side effects or drugs i.e. nausea, vomiting, respiratory depression, cardiac depression, muscle weakness, neuropathy.

Assessment of sensory, motor blockade and pain score was done at 0 min, 30 min, 1, 2, 3, 4, 6, 9, 12, 15, 18, 21, and 24 (hours).

There was no need of measuring serum Magnesium levels as the dose (100mg and 200mg) used was far less than the therapeutic dose of Magnesium Sulfate which is 300mg to 400mg per day for adults. The study dose will not cause toxic serum levels and clinical parameters were assessed (knee jerk, respiratory rate, muscle power, urine output) for early diagnosis of toxicity.

Statistical analysis was done by using SPSS software. Comparison was done by using Chi Square test. p values considered are $p > 0.05$ (not significant) $p < 0.05$ (significant) and $p < 0.001$ (highly significant)

Observations and Results

All patients completed study successfully. There was no block failure. All patients were comparable in respect to demographic data, duration of surgery, and vital parameters.

Consort Flow Diagram (Fig.1).

Onset of sensory and motor blockade was faster in group S_2 as compared to s1 and c, which is highly significant.

Duration of sensory and motor block was significantly longer in group S_2 as compared to S_1

Table 1: Demographic data of patients in three groups

Parameters	Groups			
	C	S_1	S_2	p
Age (yrs)	35.5±15.4	40.2±12	36.5±13	>0.05
Weight in Kg	60.5±5.5	58±6.6	57.2±5.5	>0.05
Male	12	15	16	>0.05
Female	18	15	14	>0.05
ASA1	20	25	19	>0.05
ASA2	10	5	11	>0.05

Table 2: Vital Parameters and Duration of Surgery

Parameters	Groups			
	C	S_1	S_2	p
Mean Heart Rate (bpm)	78.5±10	84±20	82±14	>0.05
Mean Blood Pressure(mm Hg)	84±8	90±10	88±10	>0.05
Mean Saturation (Sp02%)	99.7±0.5	99.4±0.6	99.2±0.5	>0.05
Duration of Surgery (min)	75.9±10.5	73.8±20	74.5±19.6	>0.05

Table 3: Onset of Sensory Block and Motor Block

Group	Onset of Sensory block(min)	Onset of Motor Block(min)	p Value
S2	6.5±1	9±2	P<0.001
S1	10±2.8	13±2.2	P<0.001
C	15±3	19±2.1	P<0.001

Table 4: Duration of Sensory and Motor Block

Group	Duration of Sensory Block (Min)	Duration of Motor Block (Min)	p Value
S2	550±15	440±30.2	<0.001
S1	440±10	330±15.5	<0.001
C	240±30	200±33.5	<0.001

Table 5: Duration of Analgesia

Group	Duration of Analgesia (min)
S2	540±25 min
S1	440±20 min
C	200±15 min
	p. Value <0.001

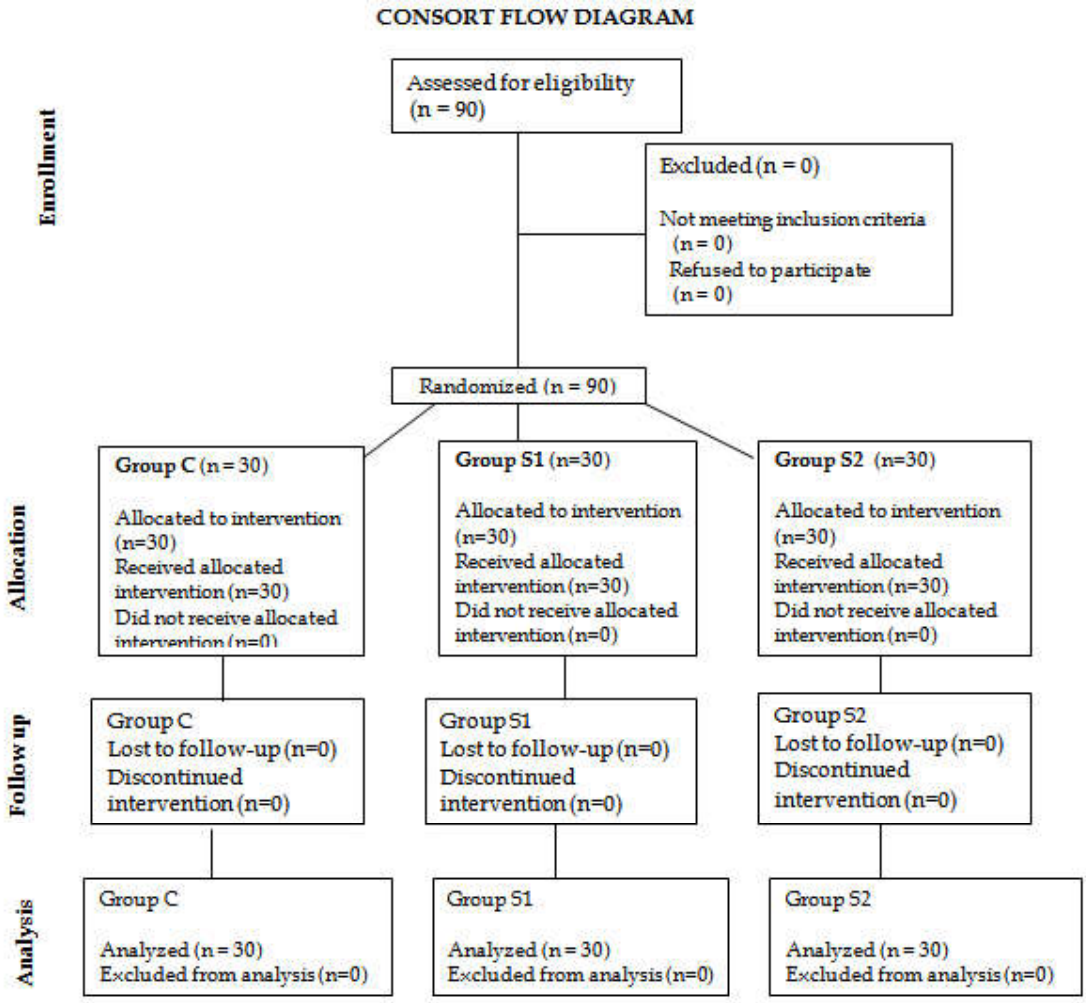


Fig. 1: Consort Flow Diagram

and C ($p<0.001$)

Duration of analgesia was significantly more in S_2 group than S_1 and C groups. Group C received maximum doses of rescue analgesics followed by group S_1 than S_2.

All patients were hemodynamically stable and no obvious side effects in perioperative period. Patients in group S_2 with $MgSO_4$ 200 mg were more comfortable than S_1 group with $MgSO_4$ 100 mg.

None of the patients experienced any symptoms and signs of Magnesium toxicity.

Discussion

The major results of our study are addition of Magnesium sulphate to local anesthetics prolongs the duration of local analgesia, fastens the onset of sensory and motor block in dose dependent manner. Higher doses have prolonged duration of analgesia without increased incidence of side effects.

There are studies on addition of $MgSO_4$ for peripheral nerve blocks. Gundez et al. [9] found that addition of $MgSO_4$ to 2% prilocaine for axillary block prolonged the duration of sensory and motor block significantly. Hypothesis for analgesic properties of Magnesium on peripheral nerves is surface charge theory. Akutagawa et al. [8] showed that modulation of extracellular magnesium concentration near the nerve bundle speeds the onset of action of local anesthetics. Mert et al. [10] reported that high concentration of divalent ions (Mg^{2+}) attracted by negative charges of surface membrane results in hyperpolarisation of nerve bundles and results in condition block. Hence more the concentration of Mg^{2+} ions, prolonged is the duration of analgesia. It supports our results that higher doses (200 mg) had more prolonged analgesia than lower dose (100 mg).

Another mechanism for analgesic property of $MgSO_4$ is NMDA receptor antagonism, which prevents central sensitisation from peripheral nociceptive stimulation. This is the basis of analgesic effect after intravenous administration and neuraxial route [11].

NMDA receptors are also found in muscles, skin [12], joint and play a role in sensory transmission of noxious signals [13]. In the study by Mukherjee et al. [14] used 150 mg of $MgSO_4$ with Ropivacaine in supraclavicular brachilal plexus block with desirable results. Whereas Bansal et al. [15] used 1.5 gm of $MgSO_4$ in intravenous regional anesthesia with excellent results and less side effects.

A R Lee [16] et al. studied 200 mg of $Mgso_4$ as adjuvant to bupivacaine with adrenaline in interscalene brachial plexus block with prolonged mean duration of analgesia which is consistent with our study.

Regarding total dose of rescue analgesics, control group received maximum doses followed by group S_1 and then S_2, which is correlating with the observation by Mukherjee et al. [14].

Prolonged analgesia with higher doses is consistent with studies by Varsha Verma et al. [17] who compared 250 mg and 125 mg $MgSO_4$ and found that 250 mg provides longer duration of analgesia as compared to 125 mg. Thus it is dose dependent.

Santosh Kumar et al. [18] reported use of $MgSO_4$ 150 mg as an adjuvant in USG guided supraclavicular block is better than Potassium Chloride for post operative analgesia.

Conclusion

After seeing the observations and results we come to conclusion that analgesic action of magnesium sulphate added as additive to bupivacaine for supraclavicular brachial plexus block is dose dependent. It also speeds the sensory and motor blockade and prolongs the duration of blockade.

$MgSO_4$ helps in reducing the rescue analgesic requirement in the post operative period making patient more comfortable.

$MgSO_4$ is economical and easily available.

Higher dose i.e. 200 mg is more effective than 100 mg without any side effects.

$MgSO_4$ can be used as an adjuvant to local anesthetics in regional blocks as it potentiates the action of local anesthetics.

References

1. Moore D, supraclavicular approach for brachial plexus block, Handbook, Thomas publishers, 1981. pp.221-41.
2. Lanz E thesia, Extent of blockade following various techniques of brachial plexus block; Anes Analg. 1983;62:55-8.
3. Brodner G et al. Regional anesthesia for postoperative pain control. AINS. 2007;42:32-41.
4. EL Saied, et al., Clonidine prolongs the effect of ropivacaine for axillary plexus block. Can J Anesth 2000;47:962-967.

5. Sarkar D et al. Comparative study on the effect of adding fentanyl and buprenorphine to local anesthetics in brachial plesus block; Clini Diag Res. 2010 Dec;2:3337-43.
6. Kapral S et al. Tramadol added to mepivacaine prolongs the duration of axillary brachial plexus block. Anesth Analg. 1999;88:853-859.
7. Faiz SH, et al. Anesthetic effects of adding intrathecal neostigmine or magnesium sulphate to bupivacaine in patients under lower extremities surgeries. PMC. 2012;17:918-22.
8. Akutegawa T et al., Magnesium enhances local anesthetic nerve block of frog sciatic nerve. Anesth Anal. 1984;63:111-6.
9. Gunduz et al. Magnesium added to prilocaine prolongs the duration of axillary plexus block. Reg Anesth pain. 2006;31:233-6).
10. Mert et al. Effect of calcium and magnesium on peripheral nerve conduction. Pol J Pharmacol. 2003 55:25-30.
11. Hwang et al. Infusion of magnesium sulphate during spinal anesthesia improves post operative analgesia. BrJA. 2010;104:89-93.
12. De Kock M F, et al. Clinical role of NMDA receptor antagonist for treatment of post operative pain. Best Pract Res Clin Anaesthesiol. 2007 Mar;21(1):85-98.
13. Renk et al. Pain facilitation and activity dependent plasticity in pain modulating circuitry, Role of BDNF, Trk B Signalling and NMDA receptors. Mol Neuro boil. 2007;35:224-35.
14. Mukherjee et al. evaluation of magnesium sulphate as an adjuvant in ropivacaine induced supraclavicular brachial plexus block. J Res Pharm Pract. 2014;3:123-9).
15. Banal et al. Comparative evaluation of magnesium sulphate and nitro glycerine as potential adjuncts to lidocaine in intravenous regional anesthesia. Int J Crit Sci. 2015;5:27-31.
16. A R Lee et al. Magnesium added to bupivacaine prolongs the duration of analgesia after interscalene nerve block. Can J Anaesth. 2012;59;21-7.
17. Versha Verma, et al., Dose finding randomised controlled trial of magnesium sulphate as an adjuvant in ultrasound guided supraclavicular brachial plexus block. IJA. 2017;61(3):250-55.
18. Santosh Kumar et al. Magnesium sulphate 150 mg as an adjuvant in USG guided supraclavicular block is better than potassium chloride for post operative analgesia. IJSR. 2017;8179.

Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; (Part - II) 6(1): 283-286
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.40

Intrathecal Fentanyl as an Adjuvant to Hyperbaric Bupivacaine in Lower Abdominal Surgeries: A Placebo Controlled Randomised Study

Naveen Kumar P[1], Umesh NP[2], Santhosh MCB[3]

[1]Assistant Professor Dept of Paediatrics, [2]Assistant Professor [3]Associate Professor Dept of Anaesthesiology, Mandya Institute of Medical sciences, Mandya, Karnataka 571401, India.

Abstract

Aim: The aim of our study was to evaluate the efficacy of intrathecal fentanyl as an adjuvant to bupivacaine on the block characteristics, hemodynamic stability and side effects in patients undergoing lower abdominal surgeries. *Methods:* Sixty patients aged between 18-60 yrs, belonging to ASA I and II posted for elective lower abdominal surgeries under spinal anaesthesiawere recruited for the study. Patients were randomly divided into two groups of thirty each. One group received 2.5 ml of 0.5% Inj. bupivacaine with 0.5 ml of fentanyl (Group FB) and the other group received 2.5 ml of 0.5% Inj. bupivacaine with 0.5 ml of normal saline (Group B). Patients were monitored for onset, duration and quality of sensory and motor block, duration of analgesia, highest dermatomal level, hemodynamic parameters and side effects. *Results:* Onset of sensory block, motor block, time to reach highest dermatomal level duration of motor block was comparable between the groups. Duration of sensory block and two segment regression was prolonged in group FB compared to Group B which was statistically significant ($p < 0.001$). Hemodynamic stability was maintained throughout intra and post-operative period in Group FB compared to Group B. Incidence of pruritis was higher in Group FB compared to Group B which was statistically significant ($p< 0.001$). *Conclusion:* Fentanyl as an adjuvant to bupivacaine provided sufficient post-operative analgesia with hemodynamic stability.

Keywords: Fentanyl; Bupivacaine; Intrathecal; Postoperative analgesia.

How to cite this article:

Naveen Kumar P, Umesh NP, Santhosh MCB. Intrathecal Fentanyl as an Adjuvant to Hyperbaric Bupivacaine in Lower Abdominal Surgeries: A Placebo Controlled Randomised Study. Indian J Anesth Analg. 2019;6(1):283-286.

Introduction

Subarachnoid block introduced by Karl August Bier is one of the oldest forms of regional blocks and is still a very commonly used procedure in our country. Subarachnoid block gives a clear advantage which is difficult to duplicate with general anaesthesia for surgical procedures below the level of the umbilicus. Over and above, one of the most useful effects of central neuraxial blockade is postoperative analgesia.

Local anaesthetics used in day to day practice are usually amides like bupivacaine, lignocaine, ropivacaine, levobupivacaine etc. Though bupivacaine has become the mainstay of spinal anaesthesia it has certain disadvantages like late onset of action and prolonged motor blockade which makes it an unsuitable agent for ambulatory

Corresponding Author: Umesh NP, Assistant Professor, Dept of Anaesthesiology, Mandya Institute of Medical Sciences, Mandya, Karnataka 571401, India.

E-mail: drumeshnp@gmail.com

Received on 31.10.2018, **Accepted on** 03.12.2018

anaesthesia [1,2,3]. The discovery of opioid receptors in the spinal cord [4] led to the use of opioids as additives along with the local anaesthetics.

Opioids are being used widely in the world with the advantage of prolonging analgesia, thus providing maximum benefit with low cost and easy techniques. Of the opioids, morphine, pethidine, fentanyl, buprenorphine etc are used. Lipophilic opioids like fentanyl and sufentanilare increasingly being administered intrathecallyas adjuncts to local anaesthetics to overcome the disadvantages of conventional doses of bupivacaine.

In our present study we evaluated the efficacy of intrathecal fentanyl as an adjuvant to 0.5% bupivacaine on sensory and motor block characteristics, hemodynamic stability and side effects due to its intrathecal administration.

Methods

Sixty American Society of Anaesthesiologists physical status I & II, patients of either gender and aged between 18-60 yrs scheduled for lower abdominal surgeries were included for the study. Ethical committee approval was obtained from Institutional Ethical committee, and written informed consent was taken from the patients. Patients with American society of anaesthesiologists physical status III and IV, with history of major cardiac, renal, hepatic, respiratory or neurological disorders and those with spine deformity, psychiatric illness, altered coagulation profile and active infection were excluded from the study.

All patients were evaluated thoroughly on the previous day of surgery and were allowed to fast overnight.Tab. Diazepam 10 mg and Tab. Ranitidine 150mg were prescribed on the night before surgery. On the day of surgery 18 G intravenous cannula was secured in non dominant hand; patients wereco-loaded with ringer lactate intravenous fluid at a rate of 15 ml/kg body weight. Standard monitoring was accomplished using electrocardiogram, non-invasive blood pressure and pulse oximetry.

Patients were randomly allocated into 2 groups by computer generated number and study drugs were prepared by one of our OT technician in colour coded syringes. Group FB (test group, n=30) received 2.5mlof 0.5% Bupivacaine heavy and 25 μg freshly drawn fentanyl citrate (0.5 ml) and Group B(control group, n=30) received 2.5 ml of 0.5% Bupivacaine heavy with0.5ml saline. Anaesthesiologists who administered the drug and patients were blinded for the study.

Subarachnoid block was performed under aseptic precautions with patients in lateral decubitus position using 25G Quincke-Babcock spinal needle at L_2-L_3 or L_3-L_4 interspace. The study solution was injected over 20-30 seconds after confirming free flow of CSF. After the intrathecal injection the patients were immediately made to lie in supine position.

Sensory level was assessed by pin prick sensation every minute till adequate sensory level was achieved and thereafter every 5 minutes for the first hour and 20 minutes till 2 segment regression. Onset of sensory block, duration of analgesia, two segment regression, time taken to reach highest dermatomal level and the highest dermatome reached were noted. Motor block was assessed by modified Bromage scale (I - free movement of legs and feet; II - just able to flex knees with free movement of feet; III - unable to flex knees but with free movement of feet; and IV - unable to move legs and feet). Onset of motor block (Bromage II), duration of motor block (regression to Bromage I) were noted.

Intravenous boluses of 6 mg mephenteramine and additional I.V. fluids were given to treat hypotension, which was defined as a systolic blood pressure <20% of preoperative value or <90 mm Hg, atropine 0.6 mg to treat bradycardia (40/min) or 30% of baseline and O_2 via face mask if pulse-oximetry reading decreased below 92%. If respiratory rate decreased to <8/min, patients were gently aroused by tapping.

Presence of side effects like pruritus, nausea, vomiting, respiratory depression and were noted intraoperatively and postoperatively. Results were tabulated and analysed.

Statistical analysis done using software SPSS version 11.5. Continuous variables were summarized as mean and standard deviation. Student unpaired 't' test was applied to onset of sensory and motor block time to highest sensory level, time for 2 segment regression, time for effective analgesia, time to motor activity. Chi-square test was applied to highest sensory level, pruritus and nausea. p value <0.05 is considered as significant (S), <0.01 is considered as highly significant (HS) and <0.001 is considered as very highly significant (VHS)

Table 1: Demographic data

	Group FB	Group B	p Value
Age in years	38.26±13.05	38.76±11.65	0.876
Male/Female	18/12	19/11	0.791
ASA I/II	16/14	17/13	0.795

Data expressed as Mean ± Standard deviation.

Table 2: Sensory and Motor block characteristics

	Group FB	Group B	P value
Onset of sensory block (min)	3.7±1.2 mins	4.0±1.1	0.371
Onset of motor block (min)	4.5±1.2	4.8±0.9	0.277
Median maximum sensory level	T4/T6/T8= 14/12/5	T4/T6/T8= 10/14/6	0.637
Time to reach highest sensory level (min)	12.9±2.8	13.08±2.2	0.789
Time for two segment regression(min)	84.3±16.33	63.3±10.72	<0.0001***
Time for rescue analgesia (min)	180.0±22.2	153.0±13.42	<0.0001***
Time for complete motor recovery (min)	148.66±20.465	142.6±18.06	0.228

Data expressed as Mean ± Standard Deviation

Table 3: Side effects

	Group FB	Group B	P value
Pruritis	10 (33.33%)	0	0.0006*
Hypotension	9 (30.00%)	12 (40.00%)	0.427
Bradycardia	2 (6.66%)	4 (13.33%)	0.393
Hypoxia	0	0	0
PONV	5 (16.66%)	8 (26.66%)	0.351

Results

All the sixty patients enrolled, successfully completed the study. Two groups were comparable with regards to age, gender and ASA grading. (Table 1).

Both the groups were comparable with respect to onset of sensory and motor block. The highest dermatomal level reached and the time taken were comparable in both the groups. (12.9±2.8 vrs 13.08±2.2, p= 0.789).

The time taken for two segment regression was prolonged in Group FB when compared to Group B and the difference was found to be very highly significant (84.3±16.33 vrs 63.3±10.72, $p < 0.0001$). The time for rescue analgesia and duration of motor block were prolonged in Group FB when compared to Group B which was found to be statistically significant (Table 2).

Both the groups were monitored for side effects both intra and post-operatively. Hypotension was seen more in Group B when compared to Group F which was found to be statistically significant. (13.33% vrs 40.0%, p= 0.02). Six patients in Group FB had pruritis but none of them in Group B. This was found to be statistically significant.

Bradycardia, hypoxia and post operative nausea and vomiting were comparable in both the groups.

Discussion

Subarachnoid block is one of the most popular techniques in our country, which unfortunately has the disadvantages of sympathetic and motor block, resulting in hypotension, bradycardia and immobility [4]. It has been a dream to produce sensory block without its accompanied complications and a major step in this path is the use of intrathecal opioids, [5] but they are not adequate anaesthetics for surgery. So local anaesthetics combined with opioids are the appropriate choice.

Studies using morphine by Semenikhin et al. [6] in 1990 concluded that addition of morphine considerably increased the quality of analgesia produced, but the incidence of late respiratory depression is more with morphine. Fentanyl, a phenyl piperidine derivative [11] and a synthetic opioid, is 100 times more potent then morphine and being more lipophilic, has fewer tendencies to cause late respiratory depression and hence, is more suitable especially in our country which has few monitoring facilities and a greater demand on them.So we decided to use fentanyl as an adjuvant to hyperbaric bupivacaine in our study.

Hunt et al. [7] showed the 6.25 μg fentanyl was capable of producing same analgesia as higher doses, with minimum side effects, after comparing 0, 6.25, 12.5, 37.5 and 50 μg doses (made to 1 ml with normal saline), with bupivacaine 0.75% in 28 parturients for caesarean section. As the dose of fentanyl increases to 0.5 to 0.75 μg/kg post operative pain relief lasts longer, but respiratory changes occur and incidence of adverse effects also increases. Hence, in our study we chose 25 μg fentanyl for non obstetric surgeries.

Hunt et al. [7] and Singh et al. [8] found onset of sensory block and motor block was not affected which was similar to our study. Though onset of sensory and motor block was hastened in our study, the difference was not significant. The time and the highest sensory level achieved were comparable in both the groups which was similar to the studies done in the past. Studies done by Singh et al. [9] and Bruce et al. [10] have shown prolongation of two segment regression which was similar to our present study findings. These findings were contradicted by the findings done by Kararmaz et al. [11].

Duration of sensory blockade was prolonged but no effect on motor block was seen in our study. This is consistent with the studies done by Belzarena et al. [12]. This could be explained by the

synergistic interaction between spinal opioids and local anaesthetics. That synergism is characterized by enhanced somatic analgesia without effect on the degree or level of the local anaesthetic-induced sympathetic or motor blockade.

Almost all the previous studies like those of Kararmaz et al. [11], Varrassi et al. [13] and Kuusniemi et al. [14] and Srivastava et al. [15] found an increased incidence of pruritus while in our study the incidence of pruritus was 33.3% (p=0.002) in test group which coincides with above studies. Hypotension was less in Group FB compared to Group B but the difference was found to be statistically non-significant. Similarly bradycardia was seen in two patients in Group FB while four in Group B which required treatment. There was no significant difference between the groups with respect to hypoxia, shivering, post-operative nausea and vomiting. Some studies like those of Singh et al. [9] and Olofsson et al. [16] found no statistically significant differences in perioperative hypotension, bradycardia, desaturation, pruritus, shivering, nausea and vomiting between test and control groups. In study of Kararmaz et al. [11] the incidence of hypotension and shivering was significant between control and test groups.

Conclusion

Addition of fentanyl to hyperbaric bupivacaine increased the duration of analgesia maintaining hemodynamic stability when compared to placebo. Pruritis was the most common side effect observed during the study which is attributed to intrathecal fentanyl.

References

1. Chilvers CR, Vaghadia H, Mitchell GW, Merrick PM. Small dose hypobaric lidocaine-fentanyl spinal anaesthesia for short duration outpatient laparoscopy. I - A randomized comparison with conventional dose hypobaric lidocaine. II-Optimal fentanyl dose. AnaesthAnalg. 1997;84(1):65-70.
2. Bruce BD, Solomon E, Levin, Hilton, Admoni H, Goldik Z. Intrathecal fentanyl with small dose dilute bupivacaine- better anaesthesia without prolonging recovery-Ambulatory anaesthesia. AnaesthAnalg. 1997;85(3):560-5.
3. Liu S, Ware P, Allen H et al. Dose response characteristics of spinal bupivacaine in volunteers. Clinical implications for ambulatory anaesthesia. Anesthesiology. 1996;85:729-36.
4. Cousins MJ, Bridenbaugh PO, Greene NM and Brull SJ. Spinal (Subarachnoid) neural blockade. In: Neural blockade in clinical anesthesia and pain management, 3rd edition, Philadelphia; J.B. Lippincott. 1998;7:203-241.
5. Stoelting RK, Hillier SC. Opioid agonists and antagonists. In: Pharmacology and physiology in anaesthetic practice. 4th edition, 2006;3:87-126.
6. Semenikhin AA, Mazaev VP. Evaluation of effectiveness of spinal anaesthetic using lidocaine combined with morphine. VestuKhirIm. 1990;144:100-102.
7. Hunt CO, Datta S, Hauch M, Ostheimer GW, Hertwig L, Naulty JS, Perioperative analgesia with subarachnoid fentanyl– bupivacaine. Anaesthesiology. 1987;67:A621
8. Singh I, Gupta M, Mahawar B, Gupta A. Comparison of effect of intrathecal sufentanil – bupivacaine and fentanyl – bupivacaine combination on postoperative analgesia. Indian J Anaesth. 2008;52(3):301-304.
9. Singh H., Cue JG, Gaines G, Geisecke AH. Effect of Intrathecal fentanyl on onset and duration of hyperbaric subarachnoid block. AnaesthAnalg. 1994;78:400.
10. Bruce BD, Solomon E, Levin, Hilton, Admoni H, Goldik Z. Intrathecal fentanyl with small dose dilute bupivacaine- better anaesthesia without prolonging recovery-Ambulatory anaesthesia. AnaesthAnalg. 1997;85(3):560-5.
11. Kararmaz A, Kaya S, Turhanoglu S and Ozyilmaz MA. Low dose bupivacaine-fentanyl spinal anaesthesia for transurethral prostatectomy. Anaesthesia. 2003;58:526-530.
12. Belzarena SD. Clinical effects of Intrathecally administered fentanyl in patients undergoing caesarean section. AnaesthAnalg. 1992;74:653-7.
13. Varrassi –G, Celleno D, Capogna – G, Constantino P, Emanuelli M, Niv-D. Ventilatory effects of subarachnoid fentanyl in the elderly. Anaesthesia. 1992;47(7):558-62.
14. Kuusniemi KS, Pihlajamaki KK. Pitkanen MT, Helenius HY and Kirvela OA. The use of bupivacaine and fentanyl for spinal anaesthesia for urologic surgery. AnesthAnalg. 2000;91:1452-6.
15. Srivastava U, Kumar A, Gandhi NK, Saxena S, Dutta D, Chandra P, Singh S. Hyperbaric or plain bupivacaine combined with fentanyl for spinal anaesthesia during caesarean delivery. Indian J Anaesth. 2004;48(1):44-46.
16. Oloffson C, Ekblom A, Skoldefors E, Waghnd B, Isusted L. Anesthetic quality during caesarean section following subarachnoid or epidural administration of bupivacaine with or without fentanyl. ActaanaesthScand. 1997;41(3):332-8.

Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(1) (Part - II): 287-295
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.41

Comparison of Midazolam and Propofol for Entropy - Guided Sedation During Regional Anesthesia

Nutan NM[1], Mubina Begum Bujapur[2], Nazeer Ahmed K[3], Sanjeev Birajdar[4]

[1]Consultant, Dept of Anesthesia, SSNMC Super Specialty Hospital, Bengaluru, Karnataka 560098, India, [2]Assistant Professor [3]Professor [4]Associate Professor Dept of Anesthesia, Al-Ameen Medical College, Vijayapura, Karnataka 586108, India.

Abstract

Background and Aims: This study aimed to compare the sedation using Entropy of Midazolam and Propofol in regional anesthesia in terms of Onset, Recovery and Side Effects. *Introduction:* Regional anesthesia is a safe and popular anesthetic technique. Effective sedation is essential for regional anesthetic technique too, to allay anxiety in the patients and improve their comfort, co-operation. Use of entropy will reduce over sedation of the patient and better monitoring of the hypnotic state of the patient. *Methods:* 100 ASA I/II adult patients undergoing elective surgery under regional anesthesia for lower abdominal and lower limb surgeries were enrolled in the study and randomly allocated into two groups. Group M: Midazolam 0.1% IV infusion started with 0.5 mg/kg/hr, Group P: Propofol 1% IV infusion started with 6 mg/kg/hr till entropy value reaches 60 then titrated to maintain entropy of 50 to 60 through syringe pump and was continued till the last suture was completed. *Results:* Dose required to reach the level of sedation was 0.5 mg/kg/hr vs 6mg/kg/hr and to maintain sedation was 0.17±0.04 mg/kg/hr vs 1.23±0.25 mg/kg/hr and onset of sedation was 4.17± 0.42 vs 2.81±0.44 minutes where as time for recovery from sedation was 9.57±2.67 vs 6.76±0.83 minutes in GroupM vs Group P respectively. Hemodynamic changes were significantly higher in Group P than Group M. *Conclusion*: Both Midazolam and Propofol can be used for sedation under regional anesthesia. Onset of action and recovery is faster with Propofol and Midazolam is more cardio stable.

Keywords: Midazolam; Propofol; IV Sedation; BIS (Bispectral Index).

How to cite this article:

Nutan NM, Mubina Begum Bujapur, Nazeer Ahmed K. Comparison of Midazolam and Propofol for Entropy - Guided Sedation During Regional Anesthesia. Indian J Anesth Analg. 2019;6(1):287-295.

Introduction

The meaning of sedation is to reduce anxiety that is anxiolysis. Patients undergoing surgery tend to be anxious. What seems like a minor procedure to the anesthesiologist and surgeon may represent a major deal to the patient. Although anxiety usually exists long before the patient is brought to the preoperative room, in some instances, it does not peak until after surgery. So the reduction of anxiety to tolerable levels is a human goal and should be attempted for every patient [4].

Sedation during regional anesthesia is desirable to minimize anxiety in the operating room environment. In addition many patients are concerned about the recall of intra operative events regardless of route of administration, patients satisfaction was reported to be higher

Corresponding Author: Mubina Begum Bijapur, Assistant Professor, Dept of Anesthesia, Al-Ameen Medical College, Vijayapura, Karnataka 586108, India.

E-mail: mubeen1983@hotmail.com

Received on 18.11.2018, **Accepted on** 13.12.2018

in the presence of more profound sedation. The long hours of surgery under regional anesthesia in supine or lateral positions can make the patient very uncomfortable. Also during orthopedic procedures, the constant awareness of the noise of instrumentation during surgical procedures creates anxiety in the patients. After sometime because of anxiety, there is persistent tachycardia, rise in blood pressure, which results in increase in blood loss during surgery [4,11].

Anxiety is also associated with significant adverse physiological responses in form of Hypertension, tachycardia, increased myocardial oxygen consumption, Gastric erosion, Intracranial hypertension and Persistent catabolism [11] which may affect the recovery. Therefore anxiolysis is a must.

Primary objectives of conscious sedation include adequate sedation with minimal risk [2,3].

Regional anesthetic techniques can be used for a variety of surgical procedures and may offer certain advantages over general anesthesia. In order to improve patients' acceptability and comfort and to reduce stress it is necessary to provide some form of sedation during the operation.

There are various methods to provide sedation during regional anesthesia, intravenous technique is widely used and suitable agents include the benzodiazepine, opiods and other IV induction agents. Currently midazolam and Propofol are considered to be the most suitable drugs [12-14,19, 22,and 23].

Entropy is an innovative monitoring modality which is designed to provide information on the state of central nervous system during general anesthesia [1,5,7-9]. Entropy monitoring is based on acquisition and processing of EEG and FEMG signals by using Entropy algorithm.

There are two parameters in Entropy

Fast reacting response entropy

More study and robust state entropy

State entropy consists of EEG signals calculated up to 32 Hz

Response entropy includes additional high frequencies up to 47 Hz

Parameters	Measurement Frequency Range	Display Range
Response entropy	0<f<47Hz	0 to 100
State entropy	0<f<32 Hz	0 to 91

Response Entropy

Response entropy is sensitive to the activation of facial muscles i.e. FEMG its response time is very fast and less than two seconds. Activation of response entropy to the painful stimuli may be interpreted as a sign of inadequate analgesia. Facial muscles may also give an early indicator of recovery.

State Entropy

State entropy is always less than or equal to response entropy. Estimation of hypnotic effects of anesthetic drugs in brain during general anesthesia is based on state entropy. State entropy is based on EEG signals. EEG can be considered as a measure for depth of anesthesia due to the following:

Entropy Range Guidelines

100	Fully awake and responsive.
60	Clinically meaningful anesthesia with low
40	probability of consciousness.
0	Suppression of cortical electric activity.

Methods

A prospective, randomized, single-blind study carried out to evaluate and compare the properties of Propofol and Midazolam in terms of hemodynamic, side effects and dosage requirement as adjuncts to spinal anesthesia. After obtaining approval from institute's Ethical Committee and patients consent, Patients ASA Grade 1 & 2, aged 19-55 years, posted for elective surgeries under regional anesthesia including lower abdominal, perineal and lower limb surgeries were enrolled in study and patients with uncontrolled Hypertension, IHD, stenotic valvular disease, pre-existing neurological deficit, sensitive to used drugs, Obesity (BMI >30) were excluded from the study.

Technique: Under standard monitoring (Pulse oximeter, NIBP and ECG). Entropy sensor was applied to the patient's forehead for Entropy monitoring. The Patients were randomly allocated into 2 groups.

The Midazolam group (Group M): Midazolam 0.1% IV infusion (dilution was done in 5% dextrose in a 50 ml syringe) started with 0.5 mg/kg/hr till entropy value reaches 60 then reduced and titrated to maintain entropy of 50 to 60 through syringe pump.

The Propofol group (Group P): Propofol 1% IV infusion (dilution was done in 5% dextrose in a 50 ml syringe) started with 6 mg/kg/hr till entropy value reaches 60 then reduced and titrated to

maintain entropy of 50 to 60 through syringe pump. Drug infusion was continued till the last suture was completed. Data was collected, Time to reach required level of sedation, Duration of surgery, Duration of infusion, HR, MAP, SpO_2 is recorded every 3 minutes till the required sedation is achieved and then every 10 minutes till the end of surgery, Time of recovery, Side effects: Nausea and vomiting: (1) No vomiting or retching. (2) Retching. (3) Occasional vomiting (1-3 times). (4) Recurrent vomiting (> 3 times). Dose to reach required level of sedation, Dose to maintain required level of sedation. Data was analyze using, Chi-square/ Fisher Exact test, Student t test. Inferential and Descriptive statistical analysis has been carried out in the present study.

Results

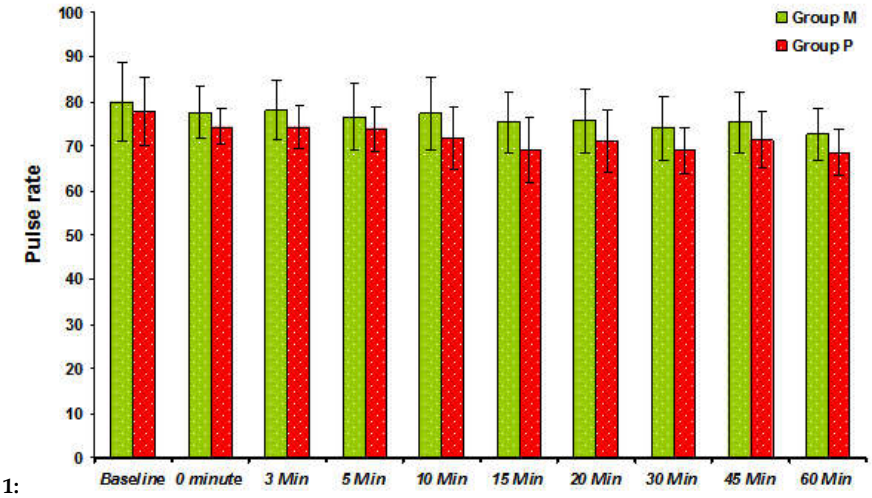
Results on continuous measurements are presented on Mean±SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance.

Table 1: Demographic Data

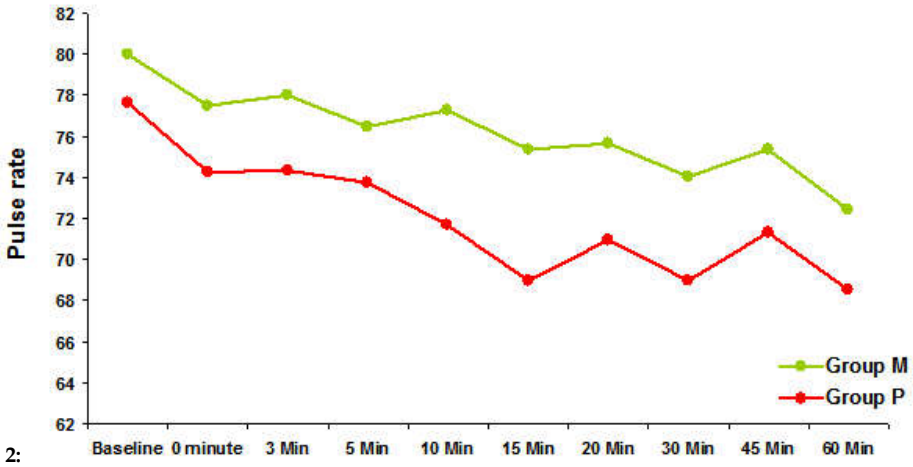
Demographic data	Group M	Group P	p value
Age, years	32.86± 5.44	34.02± 6.58	0.339
ASA Physical Status I/ II	49/1	37/13	0.001
Weight, kg	61.88±6.19	61.04±5.76	0.484

Table 2: Comparison of pulse rate in two groups of patients studied

Pulse rate	Group M	Group P	p value
Baseline	79.98±8.97	77.68±7.65	0.171
0 minute	77.52±5.87	74.30±3.91	0.002**
3 minutes	78.04±6.69	74.34±4.77	0.002**
5 minutes	76.52±7.47	73.74±4.9	0.030*
10 minutes	77.30±8.20	71.70±7.06	<0.001**
15 minutes	75.38±6.94	68.98±7.34	<0.001**
20 minutes	75.66±7.12	71.00±7.10	0.001**
30 minutes	74.06±7.05	69.02±5.32	<0.001**
45 minutes	75.36±6.80	71.36±6.50	0.003**
60 minutes	72.46±5.74	68.56±5.28	0.001**



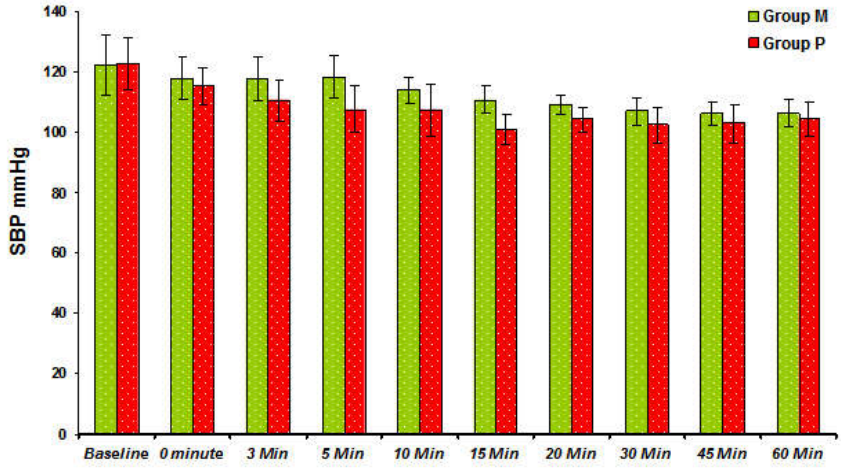
Graph 1:



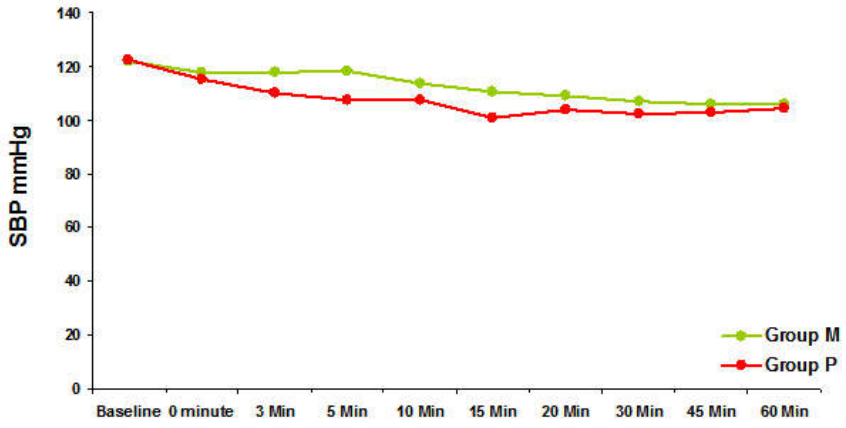
Graph 2:

Table 6: Comparison of SBP mmHg in two groups of patients studied

SBP mmHg	Group M	Group P	P value
Baseline	122.04±9.82	122.56±8.63	0.779
0 minute	117.88±7.00	115.4±6.06	0.061+
3 minutes	117.72±7.02	110.40±6.80	<0.001**
5 minutes	118.36±6.87	107.62±7.87	<0.001**
10 minutes	113.92±4.26	107.32±8.66	<0.001**
15 minutes	110.70±4.79	100.72±4.97	<0.001**
20 minutes	109.06±3.37	104.18±4.23	<0.001**
30 minutes	106.90±4.74	102.34±6.09	<0.001**
45 minutes	106.10±4.19	102.92±6.44	0.004**
60 minutes	106.18±4.71	104.54±5.81	0.124



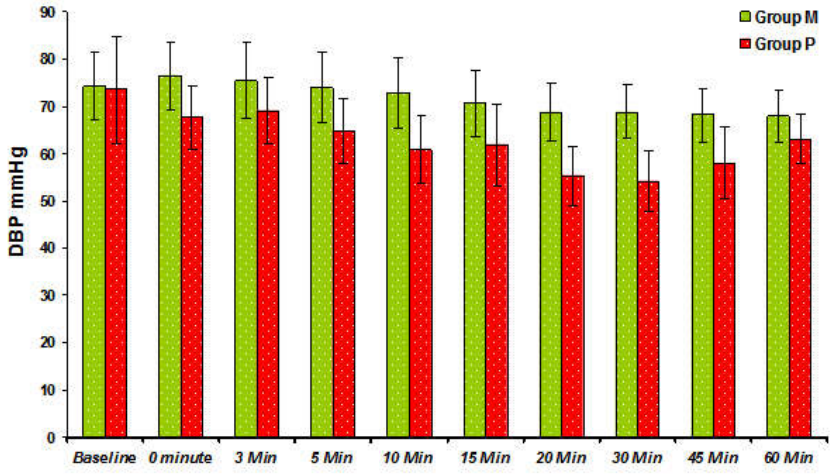
Graph 4:



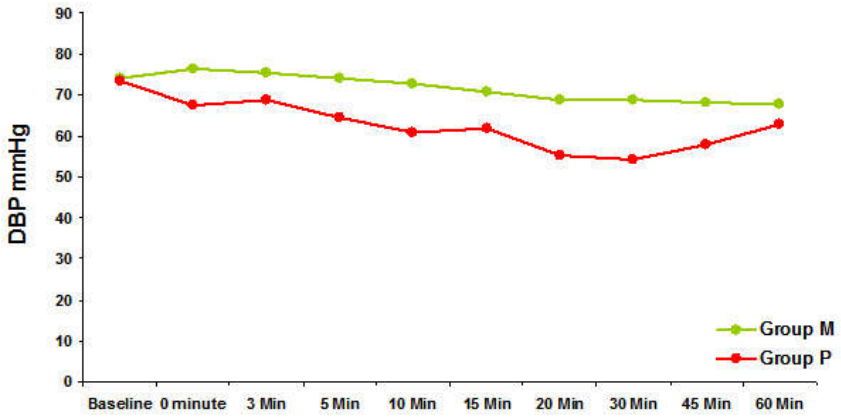
Graph 5:

Table 7: Comparison of DBP mmHg in two groups of patients studied

DBP mmHg	Group M	Group P	P value
Baseline	74.28±7.18	73.6±11.38	0.722
0 minute	76.54±7.17	67.52±6.73	<0.001**
3 minutes	75.34±8.02	68.96±6.90	<0.001**
5 minutes	74.00±7.37	64.66±6.86	<0.001**
10 minutes	72.86±7.40	60.76±7.14	<0.001**
15 minutes	70.68±6.99	61.84±8.79	<0.001**
20 minutes	68.88±6.01	55.38±6.29	<0.001**
30 minutes	68.90±5.67	54.16±6.30	<0.001**
45 minutes	68.08±5.62	57.96±7.60	<0.001**
60 minutes	67.98±5.53	63.00±5.23	<0.001**



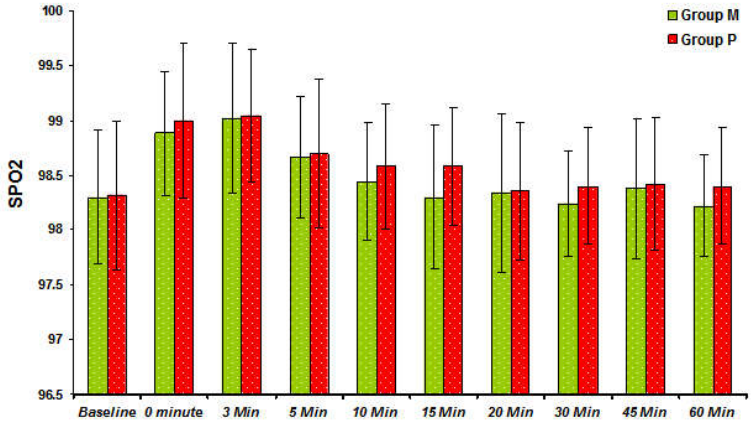
Graph 6:



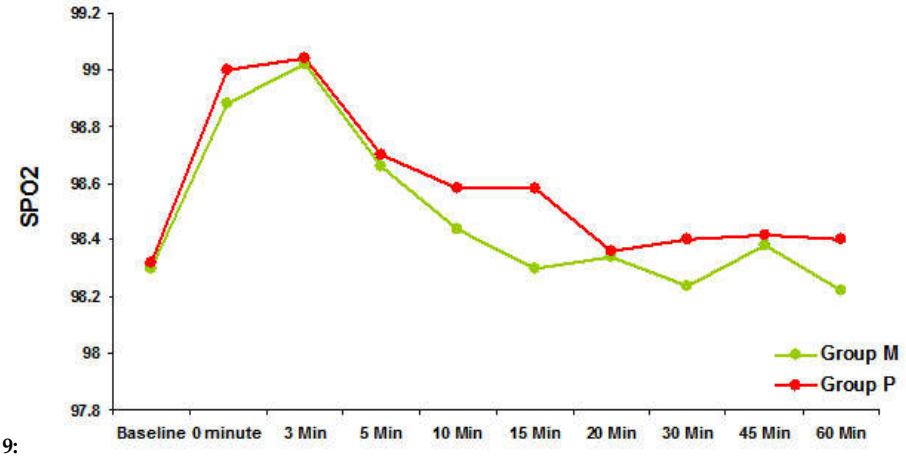
Graph 7:

Table 8: Comparison of SPO2 in two groups of patients studied

SPO2	Group M	Group P	P value
Baseline	98.3±0.61	98.32±0.68	0.878
0 minute	98.88±0.56	99.00±0.70	0.346
3 minutes	99.02±0.68	99.04±0.60	0.877
5 minutes	98.66±0.56	98.7±0.68	0.748
10 minutes	98.44±0.54	98.58±0.57	0.213
15 minutes	98.3±0.65	98.58±0.54	0.021*
20 minutes	98.34±0.72	98.36±0.63	0.883
30 minutes	98.24±0.48	98.4±0.53	0.117
45 minutes	98.38±0.64	98.42±0.61	0.749
60 minutes	98.22±0.46	98.4±0.53	0.075+



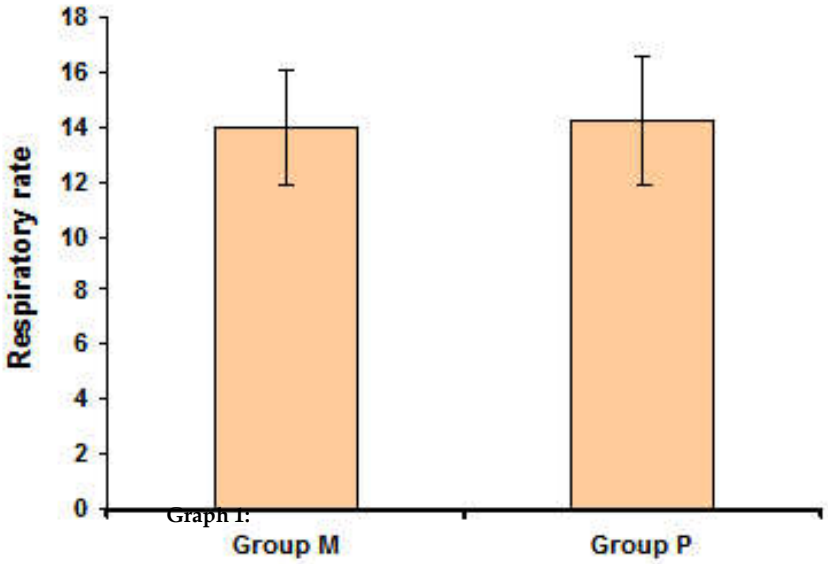
Graph 8:



Graph 9:

Table 9: Comparison of Respiratory rate in two groups of patients studied

Respiratory rate	Group M	Group P	P value
RR	14.00±2.08	14.22±2.34	0.621

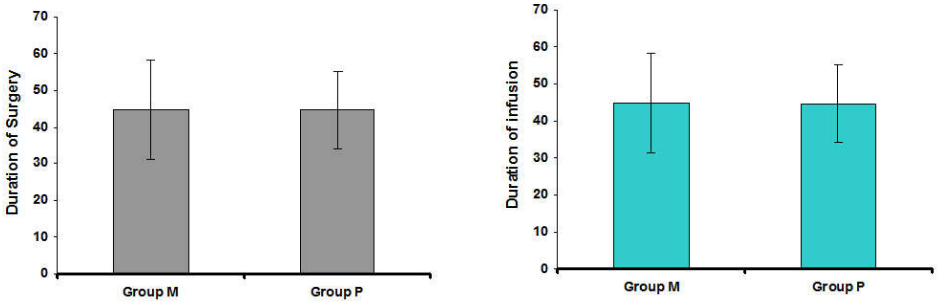


Graph 1:

Graph 10:

Table 10: Comparison of variables in two groups of patients studied

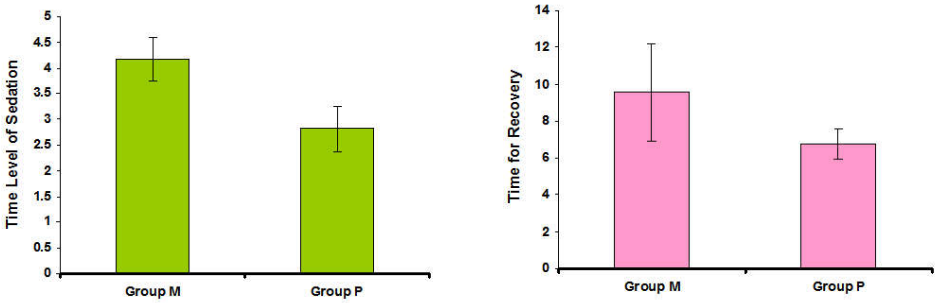
Variables	Group M	Group P	P value
Duration of Surgery	44.70±13.56	44.60±10.49	0.967
Duration of infusion	44.70±13.56	44.60±10.49	0.967



Graph 11:

Table 11: Comparison of variables in two groups of patients studied

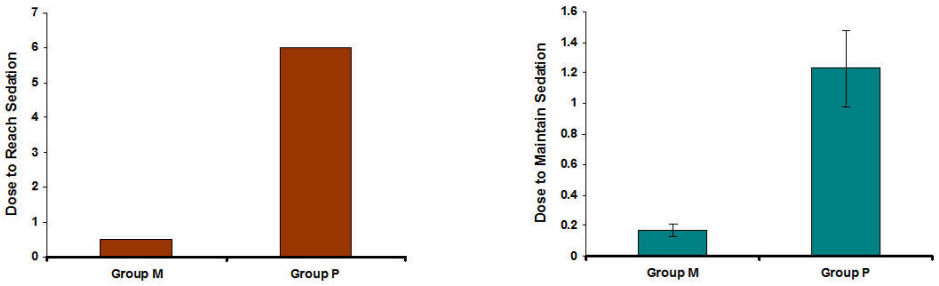
Variables	Group M	Group P	P value
Time Level of Sedation	4.17±0.42	2.81±0.44	<0.001**
Time for Recovery	9.57±2.67	6.76±0.83	<0.001**



Graph 12:

Table 12: Comparison of variables in two groups of patients studied

Variables	Group M	Group P	P value
Dose to Reach Sedation	0.50±0.00	6.00±0.00	-
Dose to Maintain Sedation	0.17±0.04	1.23±0.25	<0.001**



Graph 13:

Discussion

Regional anesthesia has become important anesthesia technique which is more popular and emerging as a safe anesthetic procedure. And most of the studies have shown that patients experience anxiety for any type of surgical procedures.

Hohener et al. report an incidence of anxiety of around 50% before receiving a regional block in their study. The study revealed Anxiety was related to higher incidence of nausea and vomiting.

Sedation is a well recognized technique to improve patients' acceptance and comfort during regional anesthesia [4]. The use of this technique is growing exponentially. Many studies have shown that use of different methods of monitoring hypnotic state of the patient is advantageous, as the incidence of side effects is lower and the amount of infused drugs is decreased [2].

Sedative-hypnotic drugs as well as narcotics are commonly used perioperatively to make regional anesthesia more tolerable for patients by reducing anxiety and providing an appropriate degree of sedation, amnesia and analgesia [3]. Dose required to reach the level of sedation in group M is 0.5 mg/kg/hr and to maintain sedation was 0.17± 0.04 mg/kg/hr and onset of sedation was 4.17±0.42 minutes where as time for recovery from sedation was 9.57±2.67 minutes which was statistically greater than Group P. In Group P, dose to reach the level of sedation was started with 6 mg/kg/ hr to reach required values of Entropy where as to maintain sedation was 1.23±0.25 mg/kg/hr. Onset of sedation in group p was 2.81±0.44 minutes where as time for recovery from sedation was 6.76±0.83 minutes. Hemodynamic changes were significantly higher in Group P than Group M more with DBP. Whereas fall in SpO_2 is more in Group M than Group P but it's not statistically significant.

E. Wilson, A. David and their group in 1990 compared the sedative effects of Midazolam and Propofol during spinal anesthesia [16]. In their study, 40 patients undergoing orthopedic surgery under spinal anesthesia received an infusion of either 1% Propofol or 0.1% Midazolam was given at a rate adjusted to maintain a similar level of sedation. The mean time to reach this required level was similar in both groups. Quality and ease of control of sedation were good in all patients.

Restoration of higher mental function was significantly faster following Propofol. Amnesia for the immediate postoperative period was significantly greater after Midazolam ($p = 0.0001$).

Hidaka S, Kawamoto M. et al., in 2005 did a comparative study on the effects of Propofol and Midazolam on cardio-vascular autonomic nervous system during spinal and epidural anesthesia [6]. Ninety eight patients were randomly divided into two groups, one group received Midazolam infusion while the other received Propofol infusion until BIS reached 75. The time to reach required sedation was 11 min in Midazolam group (Group I) while it was 6 min in Propofol group (Group II) ($p=0.0$). Fall in MABP was greater with Propofol. Recovery in with Midazolam was slower than with Propofol (18.6 ± 6.5 vs 10.10±3.65 min) ($p=0.00$). They concluded that both Midazolam and Propofol are effective sedatives, but onset and offset was quicker with Propofol, while Midazolam was more cardio stable.

In the present study it was found that both Midazolam and Propofol are effective sedatives in regional anesthesia with Propofol being faster onset and recovery from sedation where as Midazolam causes sedation which is hemodynamically more stable.

Hohener et al showed that Propofol is a substance nearest to an ideal agent for sedation during regional anesthesia because of its favorable pharmacokinetic profile with rapid onset and offset

Conclusion

Current study showed that both Midazolam and Propofol can be used for sedation in regional anesthesia. Propofol has a faster onset of action and recovery from the sedation where as Midazolam found to be more cardio stable.

References

1. Ellermann RK, Soehle M, Riese G. Entropy module ad bispectral index as guidance for Propofol – Remifentanil anesthesia in combination with regional anesthesia. PubMed. 2010 Jan;38:159-66.
2. Borgeat, Alain, Jose & Co workers: sedation and regional anesthesia. Br J Anaesth. 2009;22:678-82.
3. NYSORA: Sedation and analgesia during local and regional anesthesia. 2009;3:28.
4. D. Hoehener, S. Blumenthal & A. Borgeat. Sedation and regional anesthesia in adult patients. Br. J Anaesth. 2008;100:8-16.
5. T Ozkan-Seyhan, M Orhan Sungur. BIS guided sedation with Propofol during spinal anesthesia: influence of anesthetic level on sedation requirement. Br. J Anaesth. 2006;96:645-649.
6. Hidaka K, Kawamoto. M and colleagues. Comparison of effect of Propofol and Midazolam on cardiovascular autonomic nervous system during spinal and epidural anaesth. Indian J Anaesth. 2005;17:36-43.
7. Win Ni Ni, Harushiso F, Hikaru Kand many more compared Midazolam and Propofol for BIS- guided sedation during regional anesthesia. Anaesth Analg 2005;101:97-102.
8. R.E. Anderson, G. Barr, A-Owall et al. Entropy during Propofol hypnosis, including an episode of wake fullness. Journal of Cardiothoracic and Vascular Anesthesia. 2004;52-56.
9. Ibrahim A, Andra E and co-workers: Bispectral index monitoring during sedation with Sevoflurance Midazolam and Propofol. Anaesth. 2001;95:1151-59.
10. Krasowki MD, Nishikawa K, Nikolaeva N, et al. Methionine 286 I transmembrane domain 3 of the $GABA_A$ receptorbeta subunit controls a binding cavity for Propofol and other alkylphenol general anesthetics. Neuropharmacology. 2001;41:952-64.
11. Badner NH, Nielson WR, Munk S. & Group. Preoperative anxiety detection and contributing factors. Can. J. Anesthesia. 1999;37:444-47.
12. Ian Smith, Terri G. Monk & group. Propofol Infusion During Regional Anesthesia Sedative, Amnestic, and Anxiolytic Properties. Anesth. Analg 1994;79:313-19.
13. Alexander CM, Teller LE, Gross JB. Slow injection does not prevent Midazolam-induced ventilatory depression. Anesth Analg. 1992;74:260-64.
14. Short TG, Plummer JL, Chui PT. Hypnotic and anaesthetic interactions between Midazolam, Propofol and Alfentanil. Br J Anaesth. 1992; 69:162-67.
15. E. Wilson, A. David and group: comparison of sedative effects of Midazolam and Propofol during spinal anesthesia. Br. J Anaesth. 1990;64:48-52.
16. Sunzel M, Paalzow L, Berggren L, Eriksson I. Respiratory and cardiovascular effects in relation to plasma levels of Midazolam and Diazepam. Br J Clin Pharmacology. 1988;25:561-69.

17. Wilson E, Mackenzie N, Grant IS. A comparison of Propofol and Midazolam by infusion to provide sedation in patients who receive spinal anaesthesia. Anaesthesia. 1988;43(Suppl):91-94.
18. Larsen R, Rathgeber J, Bagdahn A, et al. Effects of Propofol on cardiovascular dynamics and coronary blood flow in geriatric patients: A comparison with etomidate. Anaesthesia. 1988;43(Suppl):25-31.
19. Mackenzie N, Grant IS: Propofol for intravenous sedation. Anaesthesia. 1987;42:3-6.
20. Taylor MB, Grounds RM, Mulrooney PD, Morgan M. Ventilatory effects of Propofol during induction of anaesthesia: Comparison with Thiopentone. Anaesthesia. 1986;41:816-20.
21. Simons P. Cocksott I Douglas E. Blood concentrations, metabolism and elimination after a sub anesthetic intravenous dose of Propofol. Postgrad Med. 1985;61:64.
22. JH. Mcclure, DT. Brown and JAW. Wildsmith: Comparison of the i.v. administration of Midazolam and Diazepam as sedation during spinal anesthesia. Br. J Anaesth. 1983;55:1089-93.
23. Arendt RM, Greenblatt DJ, deJong RH, et al. In vitro correlates of benzodiazepine cerebrospinal fluid uptake, pharmacodynamic action and peripheral distribution. J Pharmacol Exp Ther. 1983;227:98-106.

Instructions to Authors

Submission to the journal must comply with the Guidelines for Authors.
Non-compliant submission will be returned to the author for correction.

To access the online submission system and for the most up-to-date version of the Guide for Authors please visit:

http://www.rfppl.co.in

Technical problems or general questions on publishing with IJAA are supported by Red Flower Publication Pvt. Ltd's Author Support team (http://rfppl.co.in/article_submission_system.php?mid=5#)

Alternatively, please contact the Journal's Editorial Office for further assistance.

Editorial Manager
Red Flower Publication Pvt. Ltd.
48/41-42, DSIDC, Pocket-II
Mayur Vihar Phase-I
Delhi - 110 091(India)
Mobile: 9821671871, Phone: 91-11-22754205, 45796900, 22756995
E-mail: author@rfppl.co.in

Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(1) (Part - II): 297-302
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.42

To Study the N-Acetylcysteine and Vitamin C Effect on Oxidative Stress in Abdominal Sepsis and Control Patients with Different Weight Range

O Srinivas Kumar[1], M Madan Mohan Rao[2], G. Obulesu[3]

[1]Assistant Professor, Department of Anesthesiology, [2]Associate Professor, Department of General Medicine, Rajiv Gandhi Institute of Medical Sciences, Kadapa, Andhra Pradesh 516002, India. [3]Assistant Professor, Departmnent of Microbiology, Karuna Medical College & Hospital, Palakkad, Kerala 678103, India.

Abstract

"Sepsis" was characterized as the foundational reaction to infecdon, showed by at least 2 of the conditions recorded above for SIRS. "Serious sepsis" was characterized as sepsis related with organ dysflmction, hypoperfusion, or hypotension. Hypoperfijsion and perfusion abnomialities may incorporate however are not constrained to lactic acidosis, oliguria, or an intense change in mental status. *Aim:* To Study the N-Acetylcysteine and Vitamin C effect on Oxidative stress in Abdominal sepsis and controle Patients with different weight range. *Material and Methods:* The present Study was conducted in the intensive care Unit of the the Dept of Anesthesiology, Rajiv Gandhi Institute of Medical Sciences, Kadapa. *Conclusion:* Along these lines, the sex, age and weight of the patients can impact the dimension of hematological and biochemical markers in patients with sepsis. In any case, since the statistic profile of the patients in our examination was similar between the nominal control and sepsis patients and furthermore between the gatherings, it didn't impact the in general outcome.

Keywords: SOD; GRx; CRP; Catalase.

How to cite this article:

O Srinivas Kumar, M Madan Mohan Rao, G. Obulesu. To Study the N-Acetylcysteine and Vitamin C effect on Oxidative Stress in Abdominal Sepsis and Control Patients with Different Weight Range. Indian J Anesth Analg. 2019;6(1):297-302.

Interduction

"Sepsis" has its inception from a Greek word for disintegration or festering, and has been utilized in that setting since before Hippocrates (Geroulanos and Douka, 2006). In any case, in spite of the fact that the word, sepsis, has been utilized for over 2700 years, it is just moderately as of late that we have started to comprehend the pathophysiology of sepsis in any profundity (Vincent and Abraham, 2006). The rate keeps on expanding, with unsatisfactorily high death rates, not with standing the utilization of particular antibiotics, aggressive agent intercession, healthful help, and calming treatments. Not with standing high mortality, patients with serious sepsis or early septic stun invest drawn out times of energy in the ICU and are altogether more costly to treat than ICU patients without sepsis. It along these lines keeps on having noteworthy clinical and monetary ramifications and remains a zone that pulls in extreme research intrigue.

Corresponding Author: M. Madan Mohan Rao, Associate Professor, Department of Genera Medicine, Rajiv Gandhi Institute of Medical Sciences, Kadapa, Andhra Pradesh 516002, India.

E-mail: obulesu100@gmail.com

Received on 21.11.2018, **Accepted on** 13.12.2018

"Sepsis" was characterized as the foundational reaction to infecdon, showed by at least 2 of the conditions recorded above for SIRS. "Serious sepsis" was characterized as sepsis related with organ dysflmction, hypoperfusion, or hypotension. Hypoperfijsion and perfusion abnomialities may incorporate, however are not constrained to lactic acidosis, oliguria, or an intense change in mental status. Note that SIRS is a clinical disorder coming about fundamental aggravation, conceivably from a wide assortment of causes. Sepsis is the term utilized when fundamental aggravation is because of an infection. It can grow quickly. The sooner it is analyzed and treated, the better. The most incessant locales of disease prompting sepsis are the lung, urinary tract, midriff, and pelvis.

The digestion of oxygen (i.e., decrease) produces receptive intermediates called free radicals (Halliwell and Gutteridge, 1984). The electronic structure is thermodynamically more steady if electrons are matched with antiparallel turn, bringing about no net turn. In electronorbit terms, a free radical is a particle or a molecule with an unpaired electron in its external circle. By this definition, sub-atomic oxygen itself is a biradical, since it has two unpaired electrons, each arranged at an alternate pi orbital. Having a similar turn quantum number, these two electrons are situated in a parallel turn design. This turn confinement makes a circumstance in which a one-electron exchange can happen, permitting the arrangement of a particle or an iota with unpaired electron, a free radical (Halliwell and Gutteridge, 1984). lion's share of ROS are shaped amid cell breath and by enacted phagocytic cells, including neutrophils, engaged with the fiery reaction. They have physiologically fundamental jobs in mitochondrial breath, prostaglandin generation pathvi'ays and have defence.Under typical physiological conditions, a homeostatic parity exists between the arrangement of receptive oxidizing/oxygen species and their expulsion by endogenous cancer prevention agent rummaging compovmds. Oxidative pressure happens when this equalization is upset by exorbitant generation of ROS, including superoxide, hydrogen peroxidewhat's more, hydroxyl radicals, or potentially by lacking cancer prevention agent protections, including SOD, CAT, glutathione peroxidase (GPx), nutrients C and E, and glutathione (GSH). Both may happen in sepsis.

To battle the danger of oxidative worry, there exist various endogenous cancer prevention agent protections. These incorporate nutrients E and C, professional nutrient A (P-carotene), glutathione peroxidase, glutathione-S-transferase, superoxide dismutase and catalase, bilirubin, urate, and other plasma proteins. These cancer prevention agents can be partitioned into enzymatic and nonenzymatic gatherings.

The enzymatic cell reinforcements incorporate superoxide dismutase (the essential cancer prevention agent catalyst that follows up on ROS), which catalyzes the transformation of O_2" to H_2O_2 and sub-atomic oxygen; catalase, which at that point changes over H_2O_2 to H_2O and O_2, and glutathione peroxidase, which lessens H2O2 or different hydroperoxides to H_2O by oxidizing glutathione (GSH). Glutathione-S-transferase like GPX, additionally frees cells of hydroperoxides however does not follow up on H_2O_2. Re-decrease of the oxidized type of (glutathione disulfide) is then catalyzed by glutathione reductase.

The nonenzymatic cell reinforcements incorporate the lipid solvent nutrients (nutrient E, and nutrient An or P-carotene) and the water-dissolvable nutrients (nutrient C) glutathione. Vitamin E has been depicted as the significant chain-breaking cancer prevention agent in humans.Vitamin C (ascorbic corrosive), acquired principally from citrus natural products, ftinctions as a watersolubleantioxidant able to do comprehensively rummaging ROS, including the real neutrophil oxidants: H_2O_2, and hypochlorousacid.Vitamin C (ascorbic corrosive) is a powerfiil electron contributor, responding with both superoxide and hydroxyl radicals. Ex vivo contemplates demonsfrated control of cell action by exogenous ascorbic corrosive, in that the expanded adherence of, and superoxide anion generation by, macrophages from mice with endotoxic stun were bring down within the sight of ascorbic corrosive (Victor et al., 2000). In a rodent caecal ligation and cut model, exogenous adminisfration of ascorbic corrosive secured against traded off microvascular perfusion. In vitro contemplates indicated ttiat ascorbic corrosive repressed the replication of microbes and anticipated hydrogen peroxide damage to refined microvascular endothelial cells. In guinea-pigs, which, similar to people, can't integrate their own nutrient C, organization of endotoxin quickly exhausted nutrient C stores; repletion forestalled oxidative harm (Rojas et al., 1996) However, in another investigation utilizing inflision of live microorganisms, mortality was just enhanced in guinea-pigs accepting high dosages of nutrient E; high portions of nutrient C did not enhance survival (Peck and Alexander, 1991). Circling groupings of nutrient C are notably exhausted in patients with sepsis. Extraordinarily extraordinary treatment of imbued ascorbate contrasted and solid subjects was accounted for,

and organization of nutrient C related to different cancer prevention agents neglected to improve free radical-intervened harm (Galley et al., 1997).

Cowley et al., (1996), directed a forthcoming, partner think about containing fifteen patients, who were inside 16 hrs of advancement of serious sepsis and auxiliary organ dysfimction. The mean starting plasma cell reinforcement potential was lower than their range for solid volunteers ($p < 0.05$). Survivors had an underlying plasma cancer prevention agent potentialthat was more prominent than non-survivors ($p < 0.01$), and sequential subset investigation illustrated that survivors, regardless of having a low beginning plasma cancer prevention agent potential quicklyaccomplished ordinary or supranormal qualities. While plasma cell reinforcement potential moreoverexpanded in non-survivors after some time, values in this subset never achieved the ordinary run and stayed beneath qualities in survivors at record-breaking focuses considered ($p < 0.05$). Onthe premise of their information they were of the sentiment that plasma cancer prevention agent potentialat first reductions in patients with sepsis who create organ dysfimction, and it increments after some time.

Nathens et al., (2002), directed a randomized, forthcoming investigation to look at results in patients accepting cancer prevention agent supplementation (alpha-tocopherol and ascorbate) versus those accepting standard consideration. The general danger of pneumonicdismalness was 0.81 (95% certainty interim 0.60-1.1) in patients getting cancer prevention agent supplementation. Different organ disappointment was fundamentally less inclined to happen in patients getting cell reinforcements than in patients accepting standard consideration, with a relative danger of 0.43 (95% certainty interim 0.19-0.96). They inferred that early organization of cell reinforcement supplementation utilizing alpha-tocopherol and ascorbic corrosive lessens the frequency of organ disappointment and abbreviates ICU length of remain.

Aim

To assess

1. the most critical oxidative pressure marker(s) in sepsis
2. the relationship of the dimension of sepsis markers (hematological and biochemical) with that of the seriousness of sepsis
3. the cancer prevention agent operators (N-acetylcysteine and nutrient C) best in decreasing the dimension of sepsis markers (hematological and biochemical markers) in sepsis.

Material and Methods

The present study was conducted in the intensive care Unit of the the Dept of Anaesthesiology, Rajiv Gandhi Institute of Medical Sciences, Kadapa and the biochemical analyses was performed in the Dept of Biochemistry, Kadapa, Andhra Pradesh.

Sample Size

In the wake of acquiring endorsement from the Board of studies, 50 patients experiencing sepsis, conceded in the ICU and 12 nonnal individuals (as a typical control) (a sum of 62 patients) of either sex, age going between 18-55 years, were enlisted for the examination. Composed educated assent was gotten from the patients or patient's relatives.

Choice Criteria

- Age at least 18 years and not over 55 years of either sex
- Patients analyzed as peritonitis (stomach sepsis)
- Presence of at least two of criteria for fundamental incendiary reaction disorder (SIRS) and
- Presence of unequivocal site of contamination (stomach)
- Post careful septic peritonitis

Note: The criteria for the finding of SIRS is as per the following

1. Temperature more prominent than or equivalent to 38^0C or under 36^0C,
2. Pulse more noteworthy than 90 bpm,
3. Respiratory rate more prominent than 20 breaths/min or $PaCO_2$ in excess of 32 mm Hg, furthermore,
4. WBC tally more noteworthy than 12,000 for each mm or under 4000 for each mm or the nearness of in excess of 10 percent juvenile groups.

Avoidance Criteria

The accompanying patients were excluded in the examination:

- Age under 18 years,
- Glasgow trance like state scale (GCS) under 9,
- patients with un-recordable heartbeat and circulatory strain, with Acute coronary disorder, with medication overdose, with history of harming, with bum damage,

For the biochemical examination the sera were isolated from blood at the earliest opportunity by centrifugation at 2000 x g at 4^0C for 10 min in Beckman J2-M1 (Beckman instruments Inc, Palo Alto, C.A. USA) refrigerated axis. The serum got was put away in aliquots at - 20^0C until fiirther examination. 50 grown-up patients of both genders with stomach sepsis (septic peritonitis) were enlisted for the investigation. Blood tests of these patients were acquired on confirmation and broke down for assessment of haemato intelligent parameters (Hbgm%, WBC tally, and platelet tally) and serum biochemical parameters (proposed biochemical markers and serum CRP level). The qualities were then contrasted and that of nomial control patients (n = 12) to recognize the proposed markers with sigiiificant distinction by applying understudies 't' test (unpaired t-test). The markers were then registered to assess the most extreme rate change between the nomalcontrol and the sepsis patients. The information has been made reference to as mean±SD and rate (%). $p < 0.01$ has been considered factually critical.

Results and Discussion

The present investigation was intended to think about different cancer prevention agents barrier segments (enzymatic and non-enzymatic) for their power as sepsis biomarkers, differentiate them with the conventional sepsis markers and distinguish the most critical of them. The assessment was finished by looking at the dimensions of hematological and biochemical markers (proposed biomarkers and CRP) in all the sepsis patients together (NO = 50) with that of the typical control (NO = 12) subjects.

Table 1: Distribution of the patients in different weight range

Weight (kg)	Normal Control	Sepsis groups
40 - 50 Kg	2(13.3%)	6(10%)
50 - 60 Kg	6(46.6%)	20(43.3%)
60 - 70 Kg	4(40.0%)	24(46.6%)

The appropriation of patients in the scope of 40-50 kg, 50-60 kg and 60-70 kg were 2, 6, and 4, individually in nonnal control patients. Among stomach sepsis patients the dissemination was 6, 20 and 24 in the weight territory 40-50 kg, 50-60 kg and 60-70 kg, separately. There are contemplates demonstrating that oxidative harm to lipids increments and cell reinforcementsaves diminish after dietary admission (Cereillo et al., 1998; Mohanty et al., 2000) (Table 1).

Table 2: Comparison of biochemical markers between controls and sepsis patients

Parameters	Controls	Sepsis
SOD (Units/mL)	1.71 ± 0.38	7.18 ± 0.87
Catalase (Units/mL)	1.80 ± 0.60	9.83 ± 1.86
GPX (Units/mL)	0.79 ± 0.03	2.3 ± 0.41
LDH (Units/L)	70.4 ± 8.14	332.55 ± 5.64
CRP (mg/L)	7.6 ± 2.23	236.36 ± 60.40

The expansion in ROS genetation after glucose ingestion recommends that dietary admission has a task to carry out in causing expanded receptive oxygen species stack in the hefty in a way like that saw in nonnal subjects (Mohanty et al., 2000). In this way, wholesome admission is a central point influencing responsive oxygen species age and add up to oxidative load as opposed to overweight or weight. As needs be, the heaviness of the patients in the present investigation did not impact the outcomes since none of our patient was stout or overweight. Further, the mean weight of our patients went between 50 to 69 kg and it was tantamount between the nonnal control and sepsis patients and between the patients of all the five gatherings (Table 2).

Flawed procedure of blood accumulation can result in false abnormal state of cancer prevention agent. Blood gathered through extremely slender bore needle can cause haemolysis of RBC. Ill-advised division of serum from the cells can likewise impact the outcome. Be that as it may, since a standard and uniform strategy was connected for all the example gathering bothin ordinary control and sepsis patients, we accept this did not impact our outcome.From the above outcomes and exchange it very well may be induced that CRP level is the most huge and dominating biochemical marker of sepsis in our investigation.

Conclusion

Along these lines, the sex, age and weight of the patients can impact the dimension of hematological and biochemical markers in patients with sepsis. In any case, since the statistic profile of the patients in our examination was similar between the nonnal control and sepsis patients and furthermore between the gatherings, it didn't impact the in general outcome.

References

1. ACCP-SCCM Consensus Conference (1992) Definitions of sepsis and multiple organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med. 1992;20:864-74.
2. Akca S, Haji Michael P, deMedonca A, Suter PM, Levi M, Vincent JL. The time course of platelet counts in critically ill patients. Crit Care Med. 2002;30:753-6.
3. Akinci SB, Erdenl A, Kanbak M, Aypar U. Lack of effect of NAC treatment to ameliorate the progression of MOF. Saudi Med J. 2005;26:651-5.
4. Alonso de Vega JM, Diaz J, Serrano E, Carbonell LF. Plasma redox status relates to severity in critically ill patients. Crit Care Med. 2000;28:1812-14.
5. Alonso de Vega JM, Diaz J, Serrano E, Carbonell LF. Oxidative stress in critically ill patients with systemic inflammatory response syndrome. Crit Care Med. 2002;30:1782-6.
6. Amezcua-Guerra LM, Springalldel Villar R, Bojalil Parra R. Proteina C reactiva aspectos cardiovasculares de unaproteina de faseaguda. Arch CardiolMex. 2007;77:58-66.
7. Aminzadeh Z and Parsa E. Relationship between Age and Peripheral White Blood Cell Count in Patients with Sepsis, hit J Prev Med. 2011;2:238-42.
8. Andrades ME, Ritter C, Dal-Pizzol F. The role of free radicals in sepsis development. Front Biosci (Elite Ed). 2009;1:277-87.
9. Andrades M, Ritter C, de Oliveira MR, Streck EL, Fonseca Moreira JC, Dal-Pizzol F. Antioxidant Treatment Reverses Organ Failure in Rat Model of Sepsis: Role of Antioxidant Enzymes Imbalance, Neutrophil Infiltration, and Oxidative Stress. J Surg Res. 2011;167:307-13.
10. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001;29:1303-10.
11. Anup R, Apama V, Pulimood A, Balasubramanian KA. Surgical stress and the small intestine: role of oxygen free radicals. Surgery. 1999;125:560-9;174.
12. Bakker J, Zhang H, Depierreux M, van Asbeck S, Vincent JL. Effects of Nacetylcysteine inendotoxic shock. J Crit Care. 1994;9:236-43.
13. Balaban RS, Nemoto S, Finkel T. Mitochondria, oxidants, and aging. Cell. 2005;120:483-95.
14. Batra S, Kumar R, Seema, Kapoor AK, Ray G. Alterations in antioxidant status during neonatal sepsis. Aim Trop Paediatr. 2000;20:27-33.
15. Becker KL, Nyle'n ES, White JC, MuUer B, Snider RH Jr. Clinical review 167: procalcitonina and the calcitonin gene family to peptides inflammation, infection and sepsis: a journey from calcitonin back to its precursors. J Clin Endocrinol Metab. 2004; 89:1512-25.
16. Bellary SSKW, Anderson WA, Arden DA, Butterfield. Effect of lypopolysaccharide on the physical conformation of the erythrocyte cytoskeletal proteins. Life Sci. 1994;56:91-98.
17. Calandra T, Baumgartner JD, Grau GE, Wu MM, Lambert PH, Schellekens J, et al. Prognostic values of tumor necrosis factor/cachectin, interleukin-1, interferon-alpha, and interferon-gamma in the serum of patients with septic shock. J Infect Dis. 1990;161:982-7.
18. Carbonell LF, Nadal J A, Llanos MC, Hema Andez I, Nava E, DoAaz .T. Depletion of liver glutathione potentiates the oxidative stress and decreases nitric oxide synthesisi in a rat endotoxin shock model. Crit Care Med. 2000;28:2002-6.
19. Dai CH, Krantz SB, Kollar K, Price JO. Stem cell factor can overcome inhibition of highly purified human burst-forming units-erythroid by interferon gamma. J Cell Physiol. 1995;165:323-32.
20. Davies KJ, Goldberg AL. Oxygen radicals stimulate intracellular proteolysis and lipid peroxidation by independent mechanisms in erythrocytes. J BiolChem. 1987;262:8220-6.
21. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med. 2008;34:17-60.
22. Espat NJ, Helton WS. Oxygen free radicals, oxidative stress, and antioxidants in critical illness. Support Line. 2000;22:11-20.
23. Flohe L, Gunzler W. Assays of glutathione peroxidase, in: S.P. Colowick, N.O. Kaplan (Ed.), Methods Enzymology, Academic Press, New York, 1984.pp.114-121.
24. Fox ES, Brower JS, Bellezzo JM, Leingang KA. N-acetylcysteine and alphatocopherol reverse the inflammatory response in activated rat Kupffer cells. J Immunol. 1997;158:5418-23.
25. Galley HF, Davies MJ, Webster NR. Xanthine oxidase activity and free radical generation in patients with sepsis syndrome. Crit Care Med. 1996 a;24:1649-53.
26. Harman LS, Mottley C, Mason RP. Free radical metabolites of L-cysteine oxidation. J BiolChem 1984;259:5606-611.
27. Lagranha CJ, Deschamps A, Aponte A, Steenbergen C, Murphy E. Sex differences in the phosphorylation of mitochondrial proteins result in reduced production of reactive oxygen species and cardioprotection in females. Circ Res. 2010;106:1681-91.
28. Macdonald J, Galley HF, Webster NR. Oxidative stress and gene expression in sepsis. Brit J Anaesth 2003;90:221-32.

29. Noctor G, Foyer CH. Ascorbate and gluthatione: keeping active oxygen under control. Annual Rev Plant Physiol Plant MolBiol 1998;49:249-79.

Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(1) (Part - II): 303-310
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.43

Comparision of Bupivacaine with and without Clonidine as for Supraclavicular Approach to Brachial Plexus Block

P.T. Rajya Lakshmi Devi[1], B. Sai Naveena Lakshmi[2]

[1,2]Assistant Professor, Department of Anesthesiology, Siddartha Medical College, Vijayawada, Andhra Pradesh 520008, India.

Abstract

Introduction: The role of peripheral nerve blockade was expanded for management of post operative pain and chronic pain. Tramadol and fentanyl had been successfully used as adjuvant to local anaesthetic in brachial plexus block. Clonidine seems to provide analgesic benefit without major adverse effects. *Aim:* To evaluate whether additional anesthetic and analgesic effects could be derived from administration of Clonidine, an α 2- adrenergic agonist, into brachial plexus sheath. To compare the effects of Inj. Bupivacaine and Injection Bupivacaine with Clonidine as adjunct, used for Supraclavicular approach to brachial plexus block. *Materials and methods:* The study was a prospective, randomized, double-blind study. Sixty patients aged between 18 and 60 years of physical status ASA 1 and 2 undergoing upper limb surgeries lasting more than 30 minutes were included in the study. Patients were randomized into 2 groups of 30 each. All patients received brachial plexus block with 40 ml of 0.25% Bupivacaine. In addition, Bupivacaine+clonidine group received Clonidine at the dose of 2 µg/kg. *Results:* Onset of sensory blockade (time between injection and total loss of sensation to temperature) was faster in group C (22.33±4.1 min) compared to group B (27.17±3.64 min), which was statistically significant. Duration of sensory blockade (the time between injection and complete recovery from sensory disturbance) was also longer in Bupivacaine +clonidine group (524.00±83.91 minutes) compared to Bupivacaine group (339.00±57.44 minutes) and this difference was both clinically and statistically significant (p=0.001). Onset of motor blockade was faster in Bupivacaine +clonidine group (26.83±3.34 minutes) compared to Bupivacaine group (29.50±2.74 minutes).The duration of motor blockade was longer in Bupivacaine +clonidine group (524.00±83.91 minutes) compared to Bupivacaine group (339.00±57.44 min) and this difference was both clinically and statistically significant (p=0.001). Also, the time for demand of analgesics was significantly prolonged in group C (527.67±81.79 minutes) compared to group B (340.00±58.07 minutes) this difference was also statistically significant (p= <0.001). *Conclusion:* Addition of Clonidine to Bupivacaine solution for brachial plexus block can modify the action of local anaesthetic solution by its local action. There were no clinically significant side effects noticed. Hence, Clonidine can form an useful adjuvant for Bupivacaine when used for brachial plexus block.

Keywords: Bupivacaine; Clonidine; Brachial Plexus Block.

How to cite this article:

P.T. Rajya Lakshmi Devi, B. Sai Naveena Lakshmi. Comparision of Bupivacaine with and without Clonidine as for Supraclavicular Approach to Brachial Plexus Block. Indian J Anesth Analg. 2019;6(1):303-310.

Introduction

Peripheral nerve blockade is now a well-accepted concept for comprehensive anaesthetic care. From the operative suite, the role of peripheral nerve blockade was expanded for management of post operative pain and chronic pain. The recent emergence of pain management and the advantage of regional over general anaesthesia in case of emergent surgeries and the increasing importance

Corresponding Author: B. Sai Naveena Lakshmi, Assistant Professor, Department of Anesthesiology, Siddartha Medical College, Vijayawada, Andhra Pradesh 520008, India.

E-mail: sainaveenalakshmi@gmail.com

Received on 14.11.2018, **Accepted on** 03.12.2018

of outpatient (ambulatory) surgery in anesthetic practice demand a subspecialty, peripheral nerve block. Supraclavicular brachial plexus block is the preferred regional anaesthesia for upper limb surgeries. Here, the brachial plexus is presented most compactly at the proximal division or at the trunk level that provides most reliable anaesthesia for upper limb surgeries by anaesthetising the middle and lower plexus over 80% of the times (median, radial and ulnar) [1].

After synthesis of Lignocaine Lofgrens systematic study of a whole range of compounds, so laying the foundation for all subsequent studies of local anaesthetic drugs. From these studies have come derivatives of Lignocaine such as Mepivacaine, Prilocaine, Bupivacaine and Etidocaine. Local anaesthetic administered as regional nerve blocks are utilized in providing post-operative pain relief in many surgical procedures by blocking signal traffic to the dorsal horn. Certain drugs may be used as adjuncts to local anaesthetics to lower the dose of each agent and enhance analgesic efficacy while reducing the incidence of adverse reactions. Tramadol and fentanyl had been successfully used as adjuvant to local anaesthetic in brachial plexus block.

Several studies have demonstrated analgesic effects of "Clonidine", an alpha agonist, in local, spinal and epidural anaesthesia when combined with local anaesthetic Bupivacaine. This observation that Clonidine has analgesic effects at spinal level has stimulated research to examine analgesic effects in the periphery. It has direct local action on the nerve itself and facilitation of local anaesthetic action. Also, Clonidine seems to provide analgesic benefit without major adverse effects.

Aim of Study

The aim of this study is to evaluate whether additional anesthetic and analgesic effects could be derived from administration of Clonidine, an α 2- adrenergic agonist, into brachial plexus sheath.

Methods and Materials:

Sixty patients aged between 18 and 60 years of physical status ASA 1 and 2 undergoing upper limb surgeries lasting more than 30 minutes were included in the study. The study was carried out at King George hospital attached to Andhra medical college Visakhapatnam. The patients mainly included those undergoing orthopaedic, plastic and reconstructive surgeries.

Inclusion Criteria

Patients between 18 and 60 years, under physical status ASA 1 and ASA 2 scheduled for upper limb surgeries were included after obtaining ethical clearance from the Institution and informed written consent from the patients.

Exclusion Criteria

Patients with cardiovascular diseases (Ischemic heartdisease, hypertension, valvular heart disease), neuromuscular diseases, thyroid diseases, diabetes mellitus, hepatic or renal failure, pregnant women are excluded from the study.

The patients were randomly allocated into two groups: Bupivacaine + Clonidine group (n=30) and Bupivacaine group (n=30) in a double-blind fashion. Supraclavicular brachial plexus block was performed after eliciting paraesthesia. All the patients were premedicated with Intravenous Injection Midazolam 2 mg, 15 minutes prior to block.

Bupivacaine + Clonidine group (n=30) received 40 ml diluted solution containing Bupivacaine 0.25% with 2 µg/kg body weight of Clonidine for brachial plexus block.

Bupivacaine group (n=30) received 40 ml of 0.25% of Bupivacaine for brachial plexus block.

All necessary equipments and drugs needed for administration of general anaesthesia and for emergency resuscitation were kept ready in order to manage failure of block or complications occurring during procedure.

Preoperative Preparation

The study protocol was approved by the hospital ethical committee. All patients were visited and evaluated thoroughly on the day prior to surgery. During the preanaesthetic evaluation a thorough evaluation of all the systems were undertaken. The anaesthetic procedure to be undertaken including development of paraesthesia was explained to the patients and an attempt was made to alleviate the anxiety of the patient. A written informed consent was obtained. Preanaesthetic preparation of patient included a period of overnight fasting. All patients received oral diazepam 10 mg night before surgery. A meticulous airway assessment was also carried out. Routine laboratory examinations were conducted including complete haemogram, urine analysis and blood sugar, ECG and chest X-ray were done in patients above 40 years.

Procedure

Intravenous access was obtained in the limb opposite to that undergoing surgery with 18 G cannula. ECG monitoring, Pulse oximeter, Noninvasive blood pressure were connected and monitored in all the patients. The patient was placed in supine position with the head turned away from the side to be blocked. The arm to be anesthetized should be adducted, and the hand should be extended along the side towards the ipsilateral knee as far as possible. Using classic technique approach, the midpoint of the clavicle was identified and marked.

The posterior border of the sternocleidomastoid was palpated easily when the patient raised the head slightly. Palpating the belly of the anterior scalene muscle and moving towards interscalene groove with the fingers, a mark was made at approximately 1.5 to 2.0 cm above the midpoint of the clavicle. By palpating the subclavian artery at this site, the landmark was confirmed.

After appropriate preparation and injection of local anaesthetic 2% xylocaine to raise a skin wheal, 22-gauge needle was inserted at the point of entry above the midpoint of clavicle in the backward-inward-downward direction (BID). With the direction of needle was towards the first rib, Paraesthesia in the forearm or hand was elicited sometimes before and sometimes after reaching the first rib. After negative aspiration for air or blood Bupivacaine+clonidine group received 40 ml of 0.25% Bupivacaine and Clonidine 2 µg/kg. Bupivacaine group received 40 ml of 0.25% Bupivacaine.

The following parameters were observed:

1. Onset time of sensory blockade
2. Onset time of motor blockade
3. Duration of sensory blockade
4. Duration of analgesia.
5. Duration of motor block

Ramsay Sedation Scale [5]

1. Anxious, agitated or restless, or both
2. Cooperative, oriented, and tranquil
3. Responds to commands only
4. Brisk response to a light glabellar (forehead) tap or auditory stimulus
5. Sluggish response to a light glabellar (forehead) tap or loud auditory stimulus
6. No response

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean±SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance. Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups Inter group analysis) on metric parameters. Mann Whitney U test has been used to find the significance between two groups for parameters on non-interval scale.

Chi-square/Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

In the present study we analyzed statistical significance of the difference between group B (control) and group C (Clonidine). A `p` value of >0.05 meant that the difference between the groups was insignificant. A `p` value of < 0.05 was taken to be statistically significant and a value <0.01 was highly significant.

Results

Age group 21-30 are maximum in either group. Bupivacaine + clonidine group (11). Bupivacaine group (12). The average age was 35.33±10.85 years in Bupivacaine + clonidine group and 34.03±9.83 years in Bupivacaine group.

Sixty patients of either sex had participated in the study. Both groups had predominantly male patients.

The height in Bupivacaine with a mean of 156.77±4.21. Bupivacaine+clonidine group with a mean of 58.67±7.79. The maximum weight is 110 kg and a minimum of 48 kg in Bupivacaine group with a mean of 59.30±10.67 (Table 1).

Onset of blockade was group(22.33 +/-4.1 minutes) compared to Bupivacaine group (27.17+/-3.64 minutes): this difference was statistically significant (p=0.001) (Fig. 1).

It is faster in bupivacaine+clonidine group (26.83±3.34 minutes) when compared to bupivacaine group (29.50±2.74 minutes). It is statistically significant with P value <0.001 (Fig. 2).

The duration of sensory blockade in the two groups. Duration of blockade was longer in Bupivacaine + clonidine group (524.00±83.91 minutes) compared to Bupivacaine group (339.00±57.44 minutes) and this difference was statistically significant (p=0.001).

Table 1: Demographic distribution in study

Age in years	Bupivacaine+Clonidine Group		Bupivacaine Group	
	No	%	No	%
18-20	2	6.7	2	6.7
21-30	11	36.7	12	40.0
31-40	6	20.0	6	20.0
41-50	9	30.0	9	30.0
51-60	2	6.7	1	3.3
Total	30	100.0	30	100.0
Mean±SD				
Age in year		35.33±10.85		34.03±9.83
Height in cm		158.73±6.37		156.77±4.21
Weight in kilogram		58.67±7.79		59.30±10.67
Gender				
Male	24	80.0	20	66.7
Female	6	20.0	10	33.3
Total	30	100.0	30	100.0

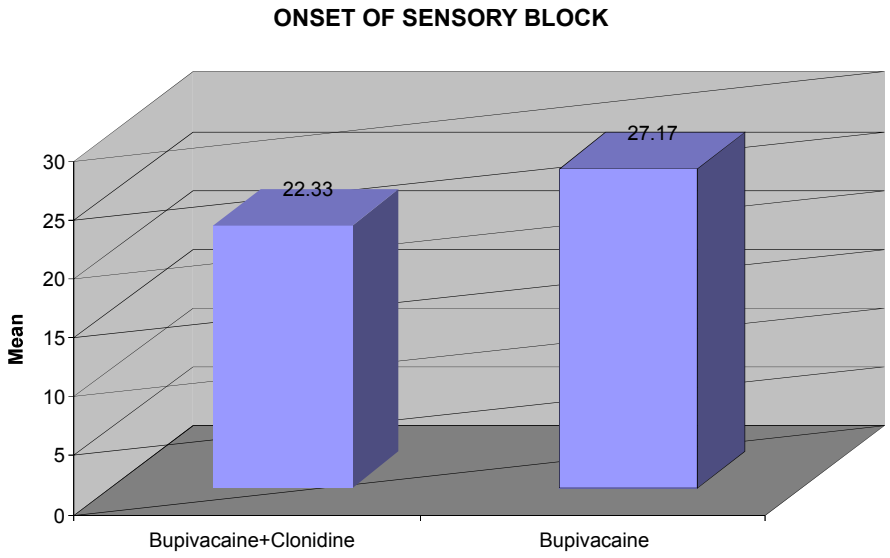


Fig. 1: Onset of sensory block

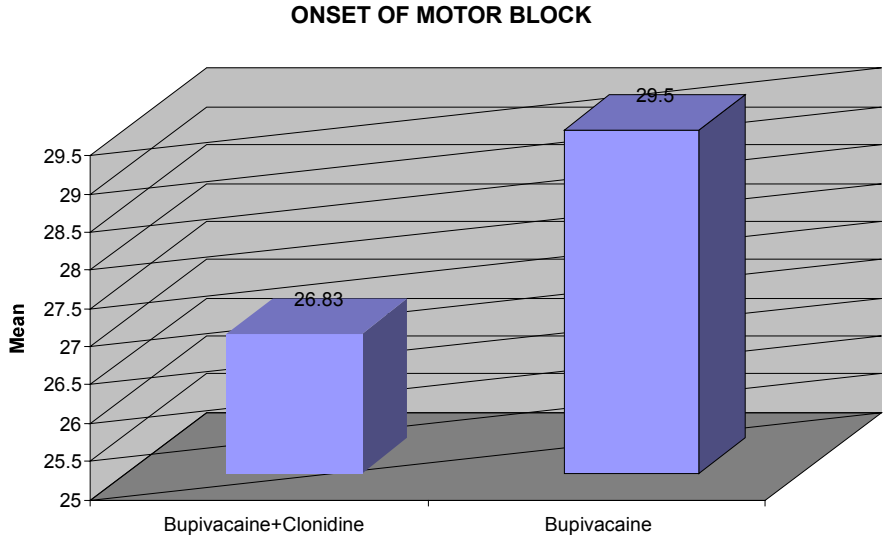


Fig. 2: Onset of motor block

Table 2: Duration of sensory block and analgesia

Duration of sensory block (minutes)	Bupivacaine+ clonidinegroup	Bupivacaine group	p value	Remark
	Mean	Mean	<0.001	Significant
	540.00±83.91	339.00±57.44		
		Duration of Analgesia (minutes)		
	527.67±81.79	340.00±58.07	<0.001	Significant
		Duration of Motor Block (minutes)		
	557.00±128.72	367.0±65.29	<0.001	significant

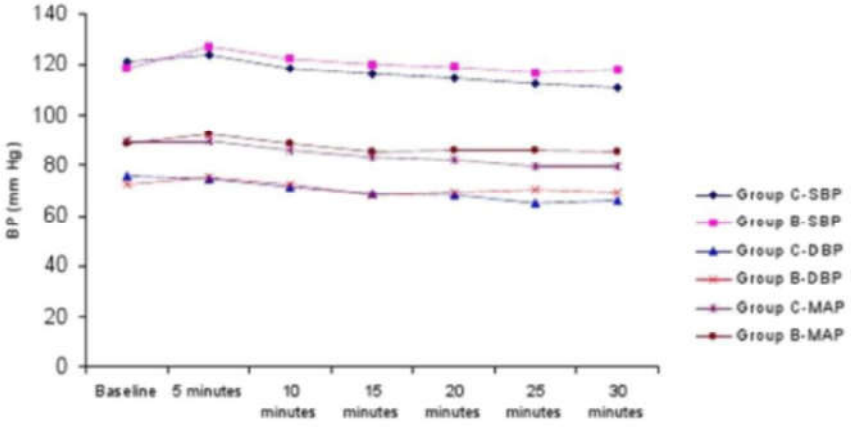


Fig. 3: Comparison of MAP (mm hg) between two groups of patients

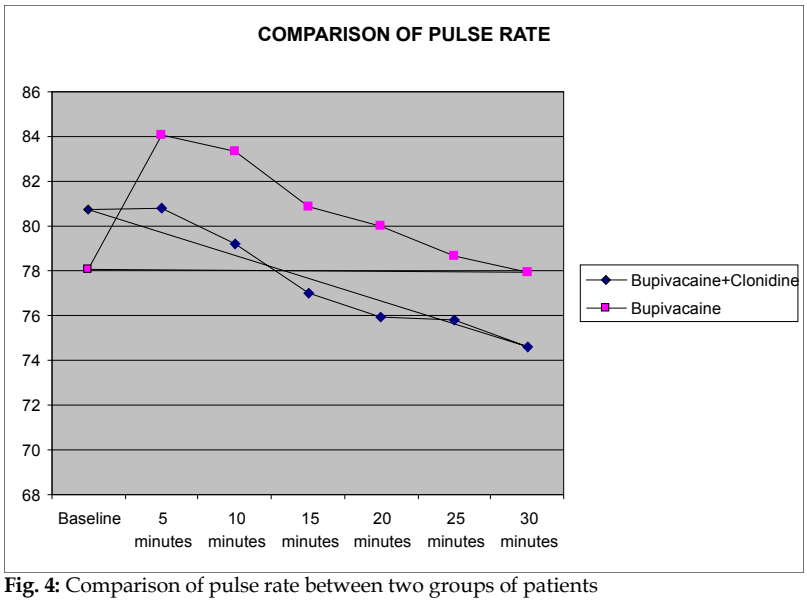


Fig. 4: Comparison of pulse rate between two groups of patients

Duration of analgesia was longer in Bupivacaine+clonidine group (527.67±81.79 minutes) compared to Bupivacaine group (340.00±58.07 minutes): this difference was clinically and statistically significant (p= <0.001).

Duration of motor blockade was longer in Bupivacaine+clonidine group (557.00±128.72 minutes) compared to Bupivacaine group (367.0±65.29 minutes) and this difference was statistically significant (p=0.001) (Table 2).

In the present study it is noticed that 10 mm of Hg mean decrease in systolic blood pressure and 9 mm Hg decrease in diastolic blood pressure in Clonidine group compared to control at 25th minute after performing brachial plexus block which is clinically and statistically not significant. Also we observed 10 mm of Hg mean decrease in Mean blood pressure in Clonidine group compared to control at 30th minute after performing brachial plexus block which is clinically and statistically not significant (Fig. 3).

Although we clinically noticed decrease pulse rate in Clonidine group by mean value of 6 beats per minute but this is not statistically significant (Fig. 4).

In our study, we found mean of 99% of saturation in both the groups this clinically and statistically not significant.

In the present study there are no observed any side effects in both the groups.

In the present study there is no undue sedation in either of groups and Ramsay Sedation score was 2 in both the groups.

Discussion

A variety of receptors mediate anti-nociception on peripheral sensory axons. The peripheral administration of appropriate drugs (Adjuncts) may have analgesic benefit and reduce systemic adverse effects. In an attempt to improve perioperative analgesia, a variety of adjuncts such as opioids, verapamil, neostigmine and tramadol have been administered concomitantly with local anesthetics into the brachial plexus sheath. The aim of this study was to evaluate whether additional anesthetic and analgesic effects could be derived from administration of Alpha-2 adrenoceptor agonist, Clonidine, into brachial plexus sheath.

The study was a prospective, randomized, double-blind study carried out at king George hospital, Visakhapatnam Sixty ASA I and II patients undergoing elective upper limb surgery lasting more than 30 minutes were included in the study. Patients were divided into 2 groups of 30 each (Bupivacaine + clonidine group & Bupivacaine group). Group C received brachial plexus block with 40 ml of 0.25% Bupivacaine and 2 μg /kg body weight Clonidine. Group B received brachial plexus block with 40 ml of 0.25% Bupivacaine. Parameters observed include onset of sensory blockade, onset of motor block, duration of sensory blockade, duration of motor blockade and duration of analgesia.

Onset of sensory block

In the present study, it is observed that onset of sensory onset was earlier in study group of Clonidine having a mean value of 22.33±4.1 min in comparison with control group having mean value of 27.17±3.64 min, which is statistically significant (p = < 0.001).

This observation well matches with study of Susmitha chakraborthy [3], onset of sensory 6.2± 0.78 minutes and 8.7±1.01 minutes in Clonidine group and control group respectively. Very short duration of onset with this study may be because of higher concentration of Bupivacaine. Similar observation was made by Gabriella Iohom [4], where the onset time of sensory block was much faster in Clonidine group, 21.3±7.2 minutes compared to that of placebo (24.7±5.5 min). A Meta-analysis was conducted by Daniel M. Popping [2] on various studies using Clonidine doses ranging from 90 to 150 μg in Brachial plexus block. He found early onset of sensory block time with an onset time of Clonidine was 12.8 minutes. In controls, average onset of time of sensory block was 15 minutes.

Onset of motor block

In the present study, it is observed that onset of motor block was earlier in study group of Clonidine having the mean value of 26.83±3.34 minutes and in comparison, the control group had a mean value of 29.50±2.74 minutes. which is statistically significant (p = < 0.001)

This observation matches well with the study conducted by Susmitha Chakraborthy [3], who had earlier onset of motor blockade in Clonidine group compared to control group, 10.6±1.36 minutes and 18.1±1.35 minutes respectively. However, Daniel M. Popping [5] had contrasting result as time for onset of motor block, quantified by using the Bromage scale. In control group mean onset time of motor block was 18.3 minutes and Clonidine had no significant impact on onset time.

Duration of sensory block

The duration of sensory blockade, in the present study was 524.00±83.91 minutes with Clonidine group and 339.00±57.44 minutes for control group, which is statistically significant (p= <0.001).

Gabriella Iohom [4] in his study, found that the duration of sensory block was longer in Clonidine group compared with placebo 275±75 versus 163±57; p = 0.04, these observation were similar to the present study. In a study conducted by Henri Iskandar [6] the median sensory block was 235 min (195–250) in the Clonidine group, compared with 150 minutes (135–160) in the control group. Giovanni Cucchiaro [7] et al. in his study on children using 0.25% Bupivacaine found significant prolongation of duration of sensory block with Clonidine group 1140 min compared to control 840 min.

Duration of analgesia

The mean time from onset of block to request of analgesia is taken as total duration of analgesia. It was 527.67±81.79 in Clonidine group and 340.00±58.07 in control group which is statistically significant p = < 0.001. According to Bernard et al. [8] in their study Clonidine reduced the use of supplementary intravenous anaesthetic agents for surgery and produced dose-dependent prolongation of analgesia, It reached a mean 770 min (range, 190-1440 min) for the largest dose 300µ which matches well with our study. According to Murphy et al., Clonidine provided an analgesic effect that lasted as long as 492 minutes which is twice the duration of placebo group 260 minutes. In Daniel M. Popping [5] study, the duration of postoperative analgesia for control group was 461 minutes where as Clonidine significantly increased the duration 584 minutes. The present study observations concurrent with study conducted by Eledjam et al. [9] in supraclavicular block with Clonidine using the dose of 150 µg and 40 ml Bupivacaine of 0.25%. The block produced with the addition of Clonidine was longer (994.2±34.2) compared to epinephrine as adjuvant (control group) 728.3±35.8.

Duration of motor block

In this present study, the duration of motor blockade was found to be 557.00±128.72 minutes in Bupivacaine + clonidine group compared to Bupivacaine group 367.0±65.29 minutes and this difference was statistically significant (p=0.001).

In the meta-analysis conducted by Daniel M. Popping [5], the average duration of motor block was 405 minutes (range, 122–728) in control group. Clonidine significantly prolonged the duration of block to 546 minutes. According to study conducted by Wolfgang Erlacher et al. [10], the duration of blockade in the Bupivacaine group was 728 minutes in control, and in comparison the duration of motor blockade in Clonidine group is 972 minutes, which are matching well with the present study.

During the present study it was noticed systolic, diastolic as well as mean arterial blood pressure were decreased but none of the patient had hypotension (defined by decrease in blood pressure by 20%). and maintained the hemodynamic parameters well within the normal range, which is similar to study conducted by Eisenach JC et al. [11] and Culebras X et al. [12]. In the present study pulse rate decreased by 6 beats but none of the patient had clinical bradycardia (decrease in basal pulse rate by 20%). which is similar to study conducted by Eisenach JC [11] et al. and Culebras X et al. [12], Also in the present study no notice was made undue sedation in either of groups and Ramsay Sedation score [5] was 2 in both the groups.

Conclusion

Clonidine is an alpha-2 agonist known to prolong the analgesic actions of local anaesthetics by acting on peripheral nerve. We studied the anaesthetic and analgesic effects of adding Clonidine into brachial plexus sheath with Bupivacaine solution in 60 patients undergoing upper extremity orthopaedic, plastic or reconstructive surgery. Patients were randomized into 2 groups of 30 each. All patients received brachial plexus block with 40 ml of 0.25% Bupivacaine. In addition, Bupivacaine + clonidine group received Clonidine at the dose of 2 µg/kg.

In conclusion, addition of Clonidine to Bupivacaine solution for brachial plexus block can modify the action of local anaesthetic solution by its local action. The dosage 2 µ/kg body weight used in the study significantly increased the duration of analgesia and muscle relaxation. There were no clinically significant side effects noticed. Hence it is concluded that Clonidine can form an useful adjuvant for Bupivacaine when used for brachial plexus block.

References

1. David LB. Spinal, epidural and caudal anaesthesia. In: Miller RD, editor. Miller's Anaesthesia. 6th ed, Vol. 2. Philadelphia: Churchill Livingstone; 2005. pp.1653-63.
2. Michael A.E. Ramsay, Acute postoperative pain management Baylor University Medical Center. 2000 July;13(3):244-47.
3. Susmita Chakraborty. Jayanta Chakraborty, Mohan Chandra Mandal, Avijit Hazra, Sabyasachi Das. Effect of Clonidine as adjuvant in Bupivacaine induced supraclavicular brachial plexus block. A randomized controlled trial. Indian J Pharmacology. 2010 Apr;42(2):74 -77.
4. Gabriella Iohom, AdnaneMachmachi, De´sire´-Pascal Diarra, Mohammed Khatouf, Sylvie Boileau, François Dap, Stéphanie Boini, Paul-Michel Mertes, and Herve Bouaziz, The Effects of Clonidine Added to Mepivacaine for Paronychia Surgery Under Axillary Brachial Plexus Block. AnesthAnalg. 2005;100:1179–83.

5. Daniel M. Popping, Elia N, Marret E, Wenk M, Tramer MR. Clonidine as an adjuvant to local anesthetics for peripheral nerve and plexus blocks a meta analysis of randomized trials. Anesthesiology 2009;111:406-15.
6. Iskandar H, Benard A, Ruel-Raymond J, Cochard G, Manaud B: The analgesic effect of interscalene block using Clonidine as an analgesic for shoulder arthroscopy. AnesthAnalg. 2003;96:260–2.
7. Giovanni Cucchiaro, Ganesh Arjun. The effects of clonidine on postoperative analgesia after peripheral nerve blockade in children. Anesth Analg 2007;104:532-7.
8. Bernard JM, Macaire P: Dose-range effects of Clonidine added to Lignocaine forbrachial plexus block. anaesthesiology. 1997;87:277–84.
9. Eledjam JJ, Deschodt J, Viel EJ, et al. Brachial plexus block with Bupivacaine, effects of added alpha-adrenergic agonists: comparison between Clonidine and epinephrine. Can J Anaesth. 1991;38: 870-5.
10. Wolfgang Erlacher, Christoph Schuschnig, Herbert Koinig, Peter Marhofer, Matthias Melischek, Nikolaus Mayer, Stephan Kapral, Clonidine as adjuvant for mepivacaine, ropivacaine and Bupivacaine in axillary, perivascular brachial plexus block. Canadian journal of anaesthesia. 2001 Feb 12;48:522.
11. Culebras X, Van Gessel E. Clonidine combined with a long acting local anesthetic does not prolong postoperative analgesia after brachial block but does induce hemodynamic changes. AnesthAnalg 2001;92:201-4.
12. Eisenach JC, De Kock M, Klimscha W. Alpha (2)-adrenergic agonists for regional anaesthesia. A clinical review of Clonidine (1984-1995). Anesthesiology. 1996;85:655-74.

Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(1) (Part - II): 311-321
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.44

Effect of Intrathecal Dexmedetomidine with Hyperbaric Bupivacaine Administered as Mixture and Sequentially in Lower Abdominal Procedures

Prithi Jain[1], Divya Vincent[2]

[1]Associate Professor Dept. of Anesthesiology, Father Muller Medical College, Mangaluru, Karnataka 575002, India, [2]Assistant Professor, Dept. of Anesthesiology, Dr. BR Amberdkar Medical College, Bengaluru, Karnataka 560045, India.

Abstract

Objectives: To compare the effects of intrathecal dexmedetomidine given mixed or sequential with 0.5% hyperbaric bupivacaine for spinal anaesthesia. *Method:* 60 patients posted for elective lower abdominal procedures were included in this study. They were randomly divided into two groups. Group M: 30 patients received 5 µg dexmedetomidine intrathecally mixed with 0.5% hyperbaric bupivacaine & group S: 30 patients received 5 µg dexmedetomidine sequentially with 0.5% hyperbaric bupivacaine. *Results:* The age and weight distribution were comparable in the two groups. The onset of sensory and motor blockade was faster in the sequential group as compared to the mixed group. The degree of sedation was higher in the sequential group. There was a statistical significance among the two groups with respect to duration of post operative analgesia with the sequential group having the longest duration. There was a statistical significant difference in the intraoperative and post operative hemodynamics with the sequential group having a lower systolic and diastolic blood pressure and lower heart rate. There were no significant adverse effects. *Conclusion:* When dexmedetomidine is given sequentially with 0.5% hyperbaric bupivacaine for spinal anesthesia, it provides early onset of sensory and motor block and prolongs the duration of anesthesia and analgesia. It also provides sedation which is unique to alpha 2 agonists, among which dexmedetomidine provides conscious sedation, with sequential groups demonstrating lower hemodynamic parameters.

Keywords: Intrathecal Dexmedetomidine; Spinal Anesthesia; Sequential Administration; Post Operative Analgesia; Sedation.

How to cite this article:

Prithi Jain, Divya Vincent. Effect of Intrathecal Dexmedetomidine with Hyperbaric Bupivacaine Administered as Mixture and Sequentially in Lower Abdominal Procedures. Indian J Anesth Analg. 2019;6(1):311-321.

Introduction

Spinal anesthesia is a type of central neuraxial blockade that is indicated for lower abdominal and lower limb surgeries. It is economical, easy to administer and very effective in producing autonomic, sensory and motor blockade.

In most cases, the drug administered is hyperbaric bupivacaine (0.5%), which is a local anesthetic (LA). For years the practice was to only administer a LA, and it was effective in almost every way in terms of motor, sensory and autonomic blockade, but it does not sedate the patient. Intravenous adjuvants can sedate the patient but if the same is given

Corresponding Author: Prithi Jain, Associate Professor, Dept. of Anesthesiology, Father Muller Medical College, Mangaluru, Karnataka 575002, India.

E-mail: drprithiballal@gmail.com

Received on 09.11.2018, **Accepted on** 03.12.2018

intrathecally, more benefit is achieved in terms of prolongation of block and effective analgesia along with sedation [1].

The need for prolonging the duration of block also arose in SAB at times as duration of block/ analgesia may be shorter than what is required for surgery. We can increase the duration of the block by adding an adjuvant, especially when increasing the dose of LA would not be ideal [1,2].

Various studies have been done by mixing adjuvants, mostly opioids with local anesthetics in order to achieve better analgesia. Some adjuvants that are used are opioids like morphine, buprenorphine, fentanyl and alpha agonists like clonidine. Studies exist on the usage of all the above drugs intrathecally and their effects on the block characteristics [3,4,5].

Studies done on the comparison of various opioids and alpha agonists intrathecally have shown the superiority of dexmedetomidine in terms of sedation, analgesia and duration of block, with very minimal reversible adverse effects [4,5].

Dexmedetomidine is an alpha 2 receptor adrenoreceptor agonist, a novel sedative-analgesic. It is a short term sedative and in addition to decreasing sympathetic tone, it attenuates the hemodynamic responses to anesthesia, reduces the anesthetic and opioid requirement. It allows psychomotor functions to be preserved while letting the patient rest comfortably. It is similar to clonidine but its selectivity for alpha 2 receptors is 8 times higher than clonidine [7].

A recent study has been done that shows clonidine given intrathecally sequentially with bupivacaine is better in terms of analgesia, duration of block and hemodynamic parameters as compared to it being given mixed with bupivacaine in the same syringe [8].

Baricity of a solution is the density of a solution in comparison to the density of human CSF (cerebrospinal fluid). It is important to note that the baricity of local anesthetics and adjuvants that are normally used are different, therefore, mixing the local anesthetic with an adjuvant can alter the baricity of the two drugs, and affects the level of motor blockade, analgesia and sedation [6].

Greene NM (1985) published a paper on the distribution of local anesthetic solutions within the subarachnoid space. He mentions that the hyperbaric solutions will alter the density of the adjuvants and reduce their spread thus blunting their efficacy [9].

Abdelhamid et al. (2013) conducted a study to determine if intrathecal dexmedetomidine was useful or not. Dexmedetomidine was added to heavy bupivacaine 0.5% intrathecally for lower abdominal surgeries. They concluded that Receiving Dexmedetomidine at a dose of 5 µg provides earlier sensory and motor blockade, less postoperative analgesic requirements, less shivering among patients of lower abdominal surgery under intrathecal anaesthesia with no sedation effect or neurologic complications [10].

The purpose of this study is to compare two different methods of administering dexmedetomidine with respect to onset and duration of sensory and motor blockade, duration of post operative analgesia, sedation and adverse effects to find a safe and more effective method of administration of dexmedetomidine.

Material and Methods

Sources of data collection

The study group comprised of patients admitted to Father Muller Medical College Hospital, Mangalore, Karnataka, for elective lower abdominal surgeries from January 2015 to June 2016.

Inclusion criteria

1. Men and women between the ages of 18-60.
2. ASA I-II
3. Scheduled for elective lower abdominal procedures.

Exclusion criteria

1. Patients with height <140 cm
2. Patients with weight >90 kgs.
3. Pregnant women
4. Patients with bradycardia (HR<50 bpm)
5. Patients with relative or absolute contraindications to spinal anesthesia
6. Emergency procedures.

Study design

A prospective, interventional randomized controlled double blinded clinical study

Sample size and sampling procedure

Sample size of 60, with sample comprising men and women in more or less equal proportion, the sampling procedure being

Group M: 30 patients receiving 5 µg dexmedetomidine (0.5 ml) + 0.5% hyperbaric bupivacaine 12.5 mg (2.5 ml) as a mixture in a single syringe.

Group S: 30 patients receiving 5 µg dexmedetomidine (0.5 ml) + 0.5% hyperbaric bupivacaine 12.5 mg (2.5 ml) sequentially in two separate syringes

Study Procedure

Patients were randomly allotted into two groups -Randomization was done using sealed envelope technique. The two drugs were sourced from the same company to avoid manufacturing differences

Pre operatively-

A baseline recording of the hematological parameters – non invasive blood pressure (NIBP), Heart rate (HR) was taken at the time of pre-anesthetic evaluation and patients were familiarized with the visual analogue scale (VAS) for pain assessment (0 being no pain and 10 being the worst possible pain). They were asked to stay nil per oral (NPO) from 12 midnight, Ranitidine 150 mg at night and the next morning (minimum 2 hrs before the surgery) was administered by the nurse in charge.

Intraoperatively-

On the day of the surgery, – non invasive blood pressure (NIBP), Heart rate (HR)-Electrocardiography, Oxygensaturation using standard pulse oximeter (SpO_2) baseline recording was taken.

After securing an 18 gauge cannula, and ensuring free flow of fluid through the vein, patients were preloaded with 15 ml/kg of either Ringer Lactate (RL) or Normal Saline (NS) depending on the diabetic status, before sub-arachnoid block (SAB).

Under strict aseptic precautions, Using a 23 gauge Quincke Babcock spinal needle through midline approach, in the lateral decubitus position, SAB was given according to the group that the patient was randomly allotted to. To maintain the same standard, the same position was also used when the two drugs were given as a mixture.

The intrathecal drugs were given in the L3-L4 subarachnoid space within 30 seconds, (including time taken for change of syringe in sequential administration) when not possible, then the L2-L3 space was used. Patients were put in supine position immediately after administration. Oxygen mask was placed on the patient, delivering oxygen at 5 L/min. Anesthesiologist other than investigator injected the drugs.

Investigator was blinded in regard to which group the patient has been allotted and the data was entered after complete evaluation in the proforma.

NIBP, HR, SpO_2 was constantly monitored throughout the surgical procedure. NIBP checked every minute for the first 5 minutes, every 2 minutes for the next 15 minutes and every 3 minutes for the next 15 minutes and every 5 minutes for the next 15 min and every 15 minutes thereafter till the end of the surgical procedure .

Sensory block assessment- pin prick with a blunt needle along the bilateral mid-clavicular line Time taken to reach T 10 dermatome was recorded (onset)

Motor block assessment- for this purpose we used the modified Bromage scale [11]. Assessment for repeated every minute till complete block-bromage 0

For sedation assessment- Modified Ramsay sedation score (RSS) [12]

Hypotension (>30% of baseline fall or <90 mmhg SBP) was treated with 6 mg of mephenteramine with co loading of IV fluids. Dosing was repeated if required. Bradycardia (HR<50 bpm) was treated with IV atropine 0.3-0.6 mg. this was repeated if required. Desaturation (SpO_2 <95%) was dealt with by supplementing oxygen and ensuring free airway.

Post operatively-

After the patient was shifted to the post operative ward, the NIBP, HR, SpO_2, Ramsey Sedation score and VAS was recorded at 15 min, 30 min, 60 min and every hour till 6 hours post spinal block (follow up). Time taken to reach S1 dermatome was recorded (sensory block regression). Time taken for motor block to regress to modified Bromage 0 also was noted. Time for first analgesic request also was noted.

Patients complaining of nausea or vomiting were given injection ondansetron 0.15 mg/kg i.v. In case of complaints of pain; IV tramadol 100 mg rescue doses was given.

Observations and Results

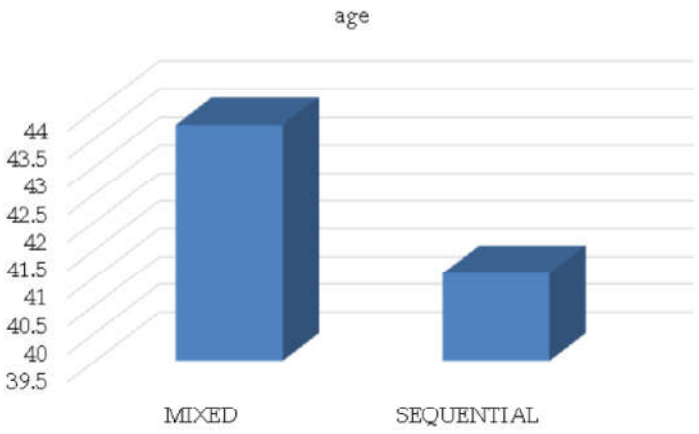
Statistical analysis

Power analysis from similar studies suggest that a sample size of 30 patients/group is required to get the power of study to 80%, with 0.05 level of significance. All the data was fed into the IBM SPSS software, mean and standard deviation was used for continuous data and median for non parametric

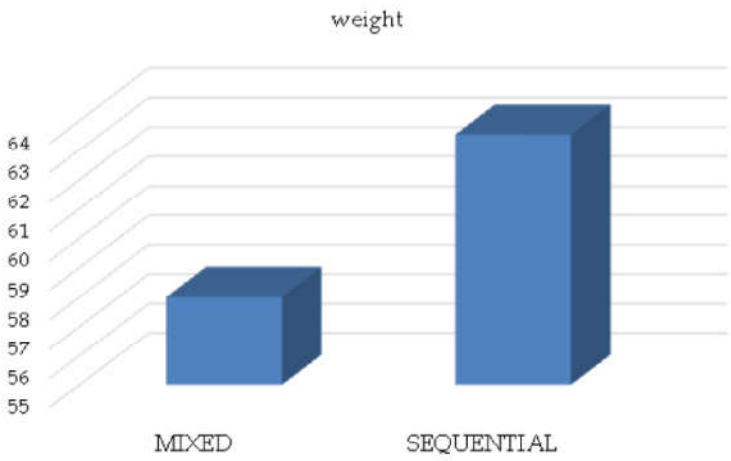
data. The two groups were compared using paired t test in terms of hemodynamics. Level of block achieved was calculated using chi-square test. The sedation was compared with the help of chi square test. Age and weight compared using independent t test. p values of < 0.05 and Confidence intervals of >95 if achieved was considered significant.

Results

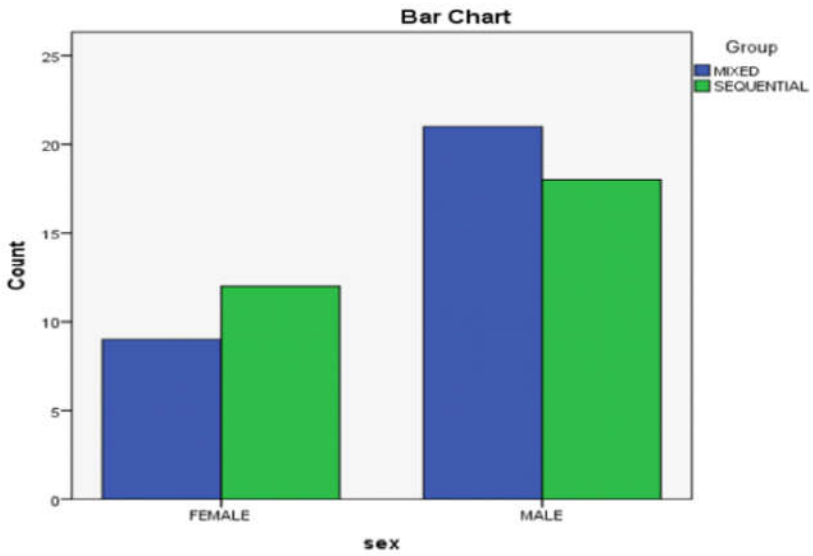
- The demographic profile was comparable in both groups.
- Earliest onset of sensory blockade was observed in the sequential group within 1 min as compared for mixed 1-1.5 mins.
- Onset of motor blockade was observed earliest in the sequential group within 1-1.8 mins, followed by mixed group which took 1.7-2 mins.
- Maximum level of sensory block reached (T8) was higher in sequential group.
- Regression of sensory blockade took longer in sequential group with a mean of 12623 min followed by mixed group which took 104.83 min.
- Regression of motor blockade took longer in sequential group which was 138.33 min followed by mixed group which was 133.87 min on an average.
- Highest degree of sedation was seen in sequential group.
- Intraoperative hemodynamics were lower in sequential group.
- Post operative hemodynamics were lower in sequential group.
- Duration of analgesia was longer in sequential group.
- VAS was lower in sequential group.
- Incidence and severity of bradycardia was higher in sequential group, but not deleterious.
- No significant adverse effects.



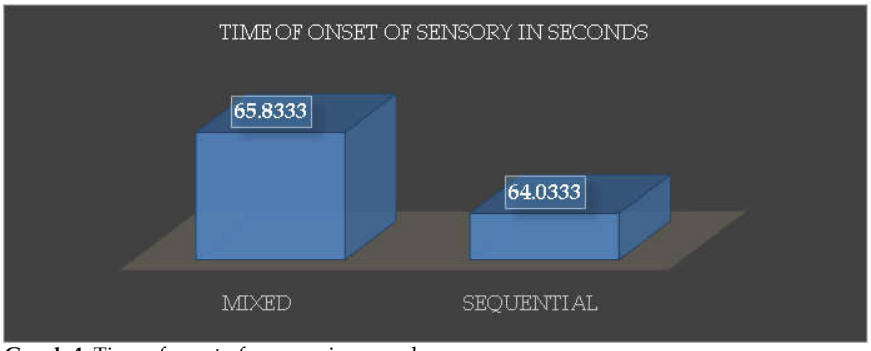
Graph 1: Bar Chart representing the distribution of age in both groups



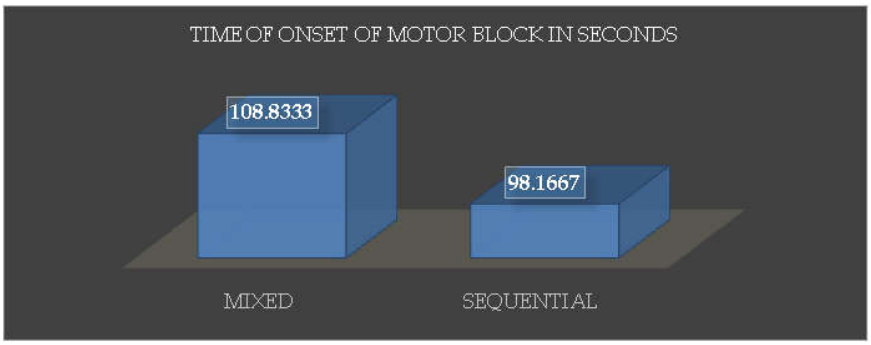
Graph 2: Histogram representing the distribution of weight in both groups



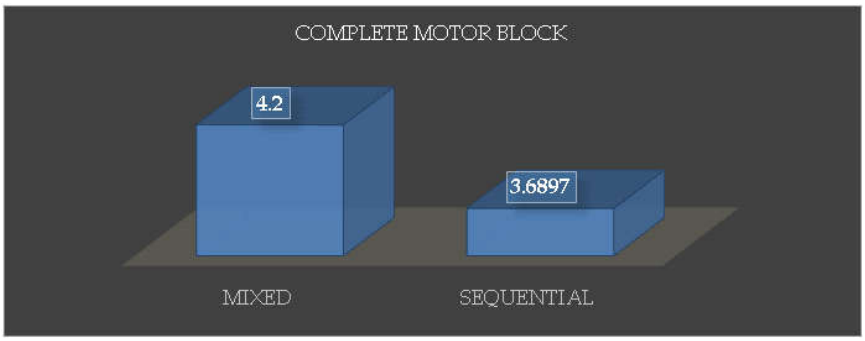
Graph 3: Gender distribution among the two groups



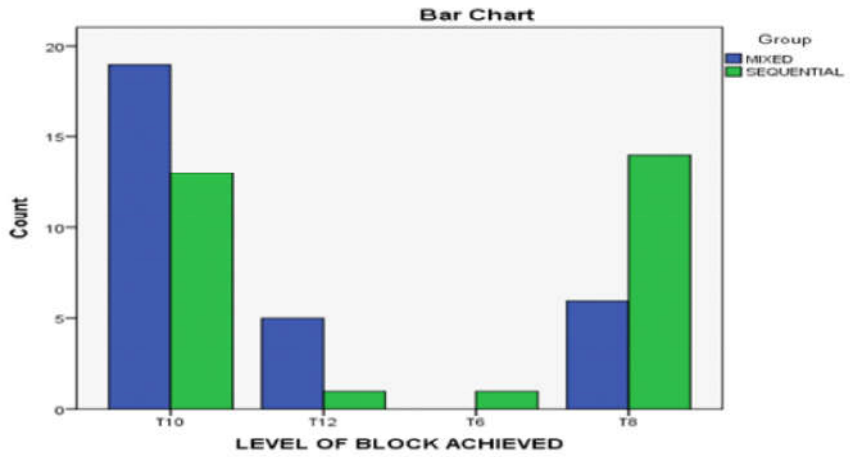
Graph 4: Time of onset of sensory in seconds



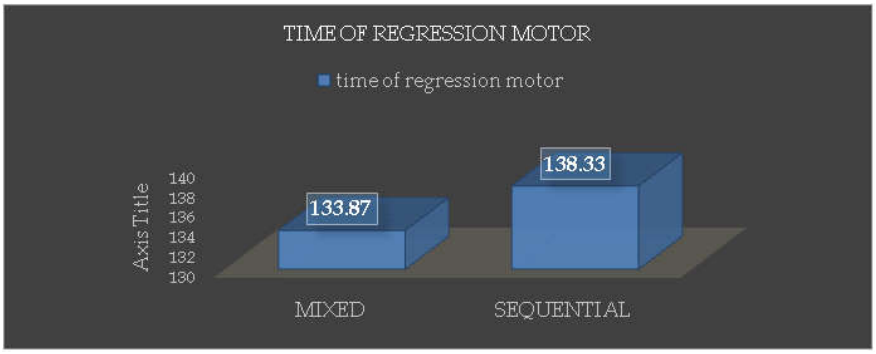
Graph 5: Time of onset of motor block in seconds



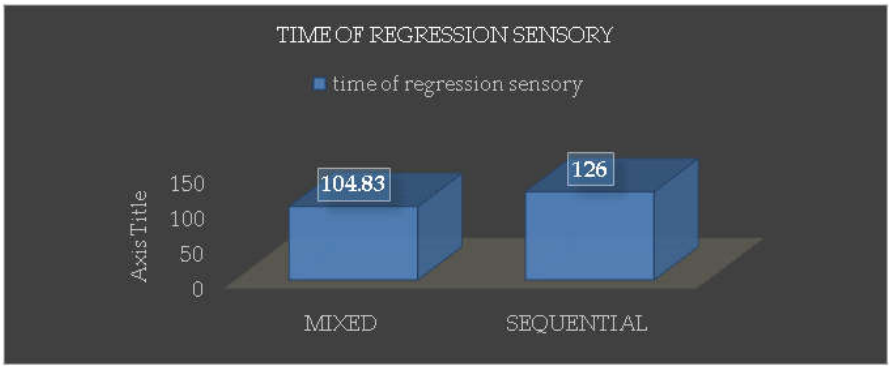
Graph 6: Complete motor Block



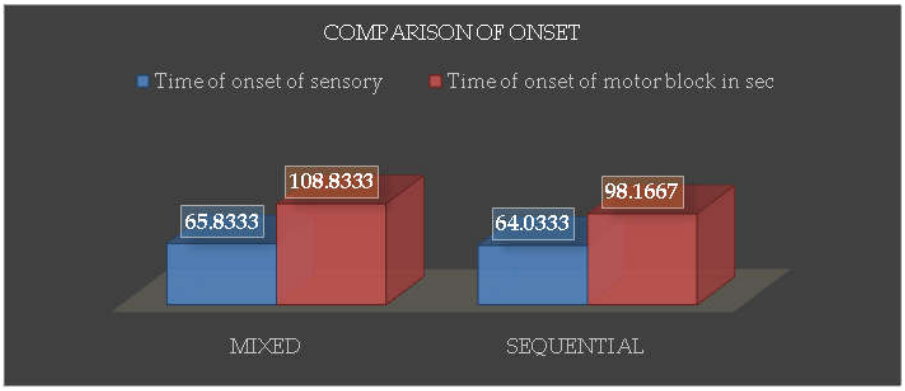
Graph 7: Bar chart representing the level of block achieved



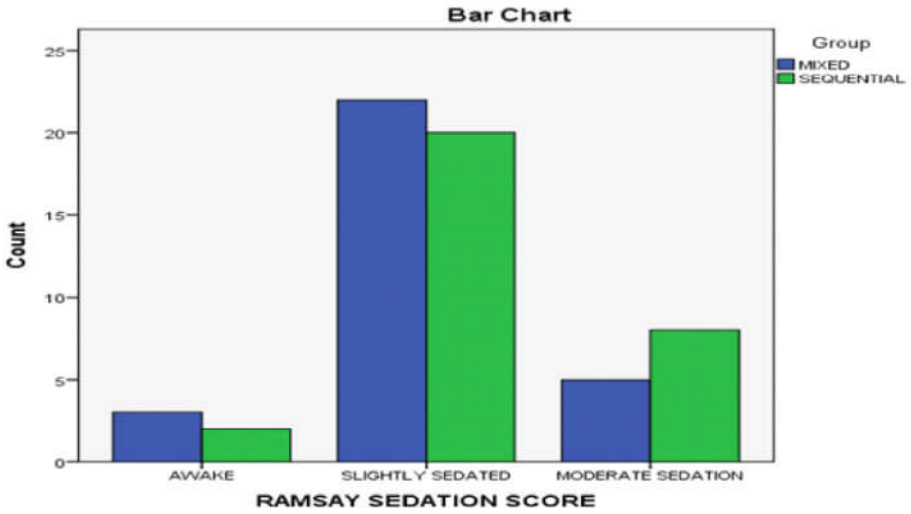
Graph 8: Time of Regression Motor



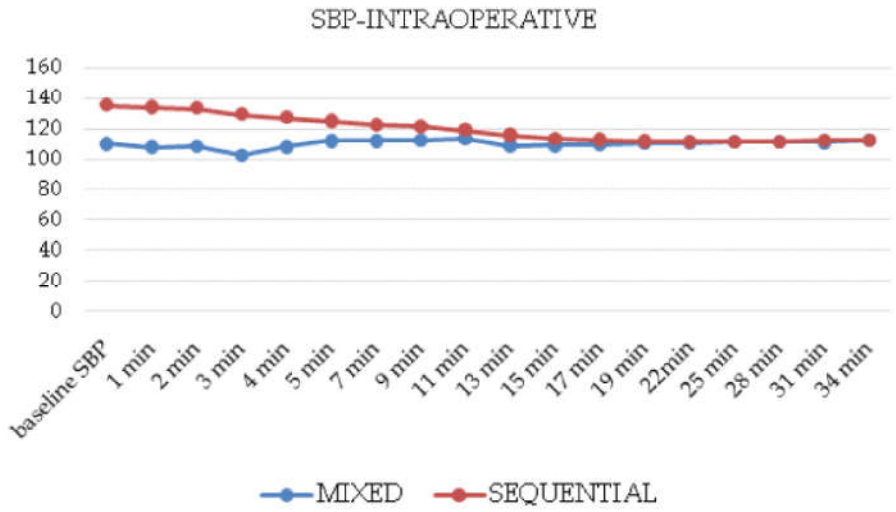
Graph 9: Time of Regression Sensory



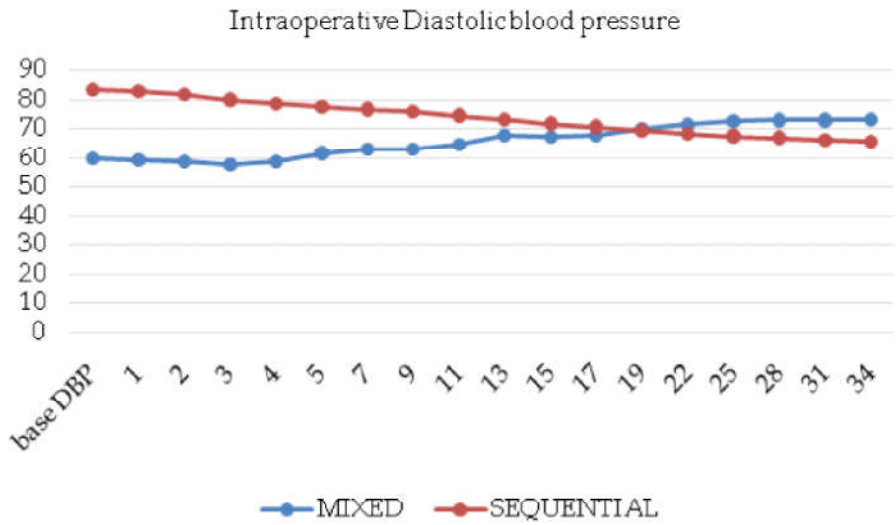
Graph 10: Comparison of onset



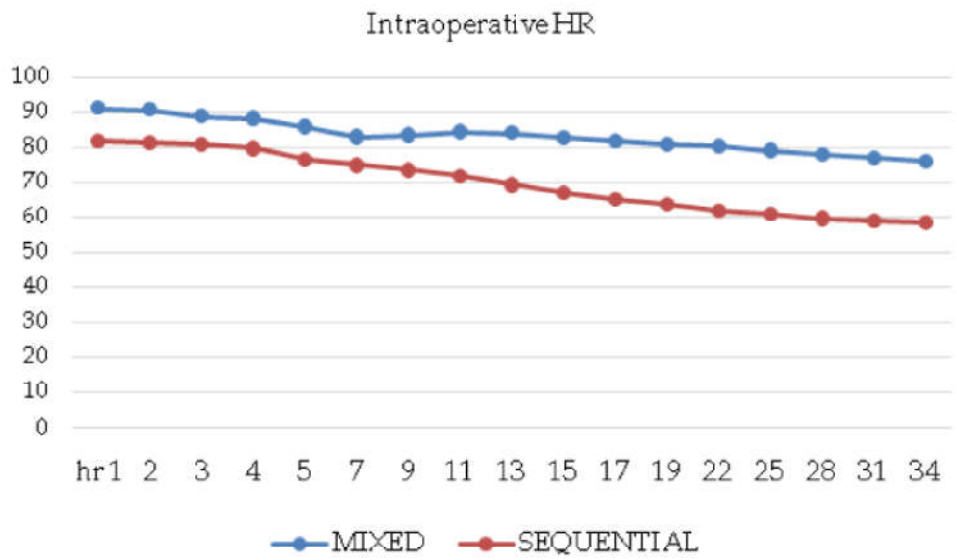
Graph 11: Bar chart representing the levels of sedation among the two groups



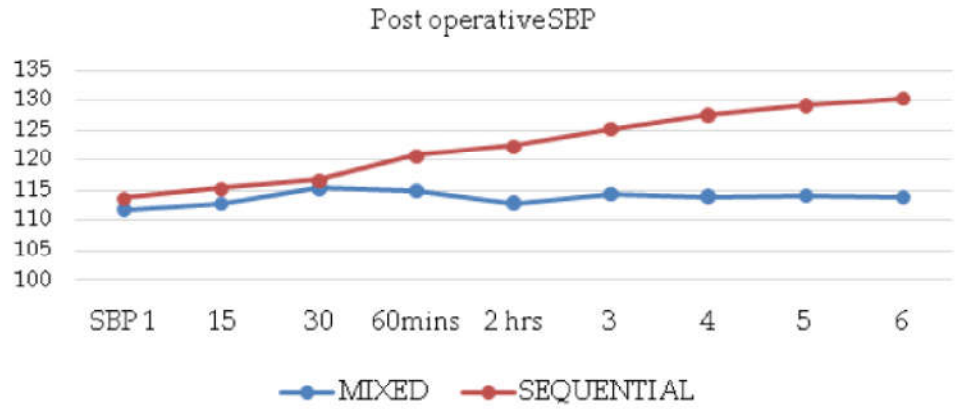
Graph 12: Intraoperative SBP among the two groups



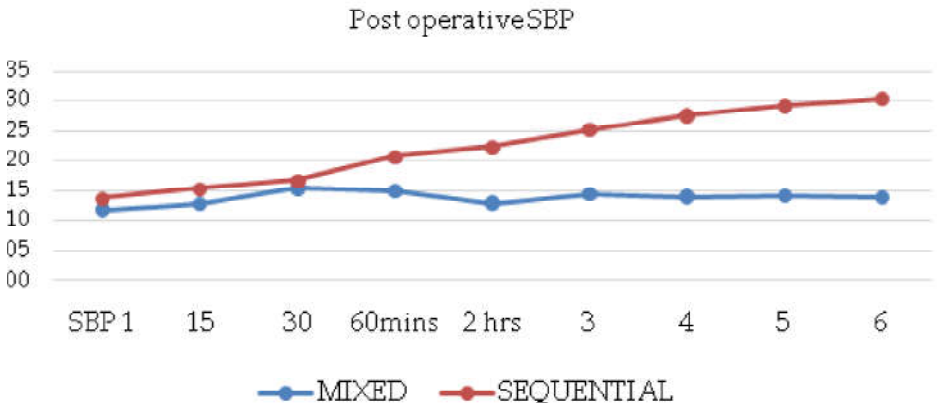
Graph 13: Comparision of the intraoperative Diastolic blood pressure



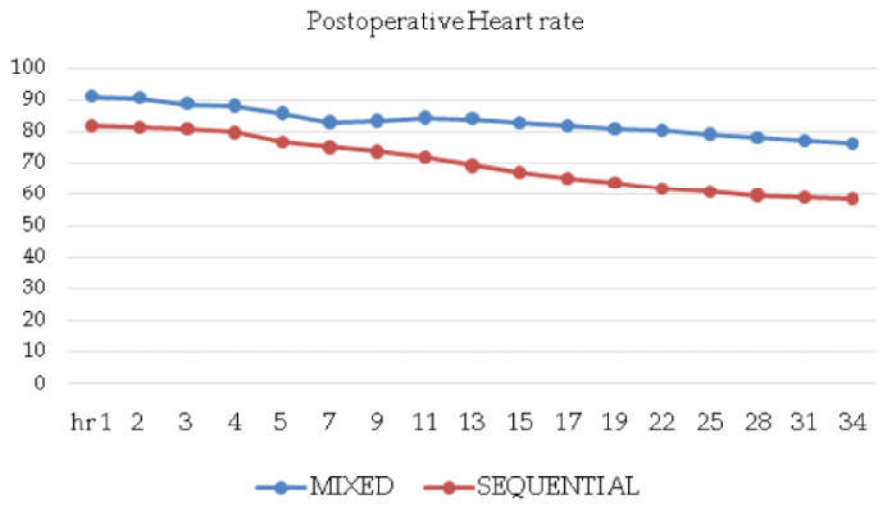
Graph 14: Comparison of Intraoperative heart rate



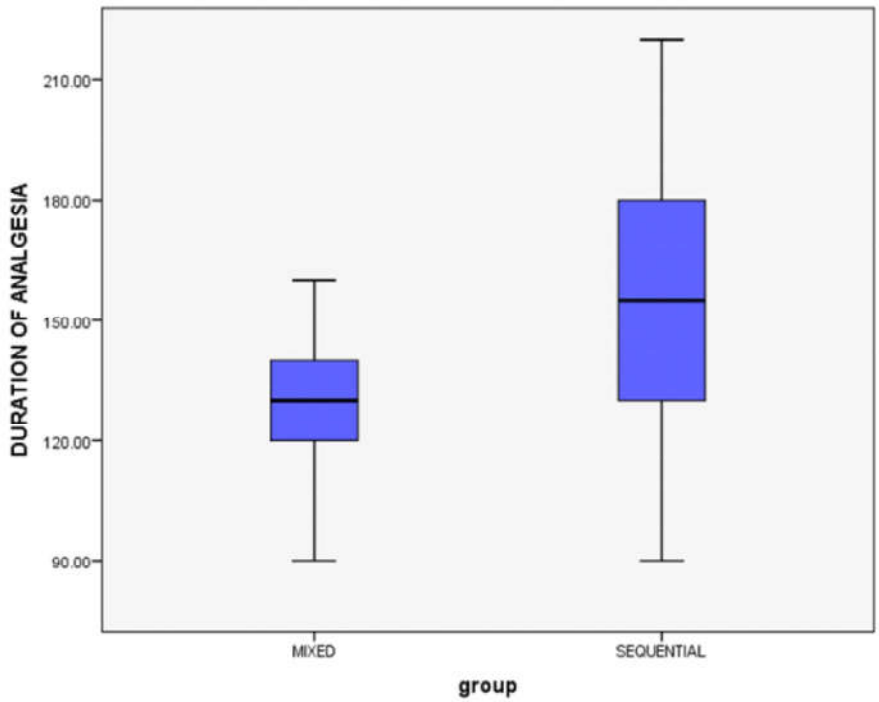
Graph 15: Mean Post-operative Diastolic blood pressure



Graph 16: Comparison of Postoperative DBP



Graph 17: Postoperative Heart rate



Graph 18: Box Plot showing Mean duration of post operative analgesia

Discussion

The dosage of intrathecal dexmedetomidine was decided after careful review of the various studies which use different doses of dexmedetomidine and the effects of the different doses.

It was observed that 5 of intrathecal dexmedetomidine produced effective sensory block and duration of anesthesia, along with sedation and lesser incidence of adverse effects like bradycardia and hypotension.

Comparison of the age and weight between the two groups shows that the groups were comparable, hence giving leverage to study findings.

The onset of sensory block was studied among the two groups, The test showed that the time of onset of sensory block is faster in sequential group. This shows that dexmedetomidine causes early onset of sensory block.

Comparison of the Time of onset of motor block and Complete Blockin sec between the two groups shows that Time of onset of motor block in seconds is faster in sequential group.

Comparison of the time of regression of motor

block between the two groups shows that time of regression of motor block is higher in sequential group shows that the time for regression is delayed while using dexmedetomidine in either mixed or sequential form.

Comparison of the time of regression sensory between the two groups shows that time of regression sensory is higher in sequential. This proves that dexmedetomidine does prolong the duration of sensory blockade which is statistically significant, especially when given sequentially.

In the mixed group, 10% of patients were awake, 73.3% were slightly sedated and 16.7% were moderately sedated.

In the Sequential group, 6.7% were awake, 66.7% were slightly sedated and 26.7% were deeply sedated.

This shows that there was significant amount of sedation in both groups with higher level of sedation seen in the sequential group.

The mean systolic blood pressure among the two groups was compared and was found that the sequential group had a higher SBP which was statistically significant.

By 30 minutes of the procedure, the two groups SBP was comparable.

The mean diastolic blood pressure was higher in the sequential groups, which was statistically significant.

The intra operative heart rate was higher in the mixed group compared to sequential group which was statistically significant.

The systolic blood pressure (SBP) and DBP in the post operative period was comparable till 30 minutes post operatively. And thereafter the BP was higher in sequential group which was statistically significant. This shows that giving DXM mixed potentiates the fall in SBP seen with local anesthetics, whereas given sequentially increases duration of analgesia without much fall in systolic blood pressure.

The post operative heart rate was higher in the mixed group when compared with the sequential group which was statistically significant, in other words, sequential administration of DXM causes more bradycardia.

The median duration of analgesia is higher in the sequential group with 155 min average. This was an important part of the study. This is significantly higher when compared to the other studies control group with an average of 125 min.

All the 60 patients showed VAS < 4 in the first 120 minutes. At the 180th time interval, 2 patients from mixed group and 1 patient from sequential group experienced VAS > 4 and were administered the rescue analgesic. This corresponds with good postoperative pain relief.

The incidence of nausea and vomiting were not significant in either group. No other adverse effects were seen except for two patients who had a heart rate of 39 and dropping, who needed Inj. Atropine 0.6 mg in the post operative ward.

Conclusion

Based on the findings of the study, we can conclude that for elective lower abdominal procedures, intrathecal dexmedetomidine 5, given sequentially with 0.5% hyperbaric bupivacaine provides faster onset of sensory and motor blockade, longer duration of anesthesia and analgesia along with sedation, when compared to the mixed group. Significant bradycardia was observed, that was not deleterious to the patient, there were no other significant side effects.

Abbreviations

DXM- Dexmedetomidine

DBP- DiastolicBlood Pressure

SBP- Systolic blood pressure

VAS- Visual Analogue scale

LA- Local Anesthetic

References

1. Honeher D, Blumenthal S, Borgeat A. Sedation and regional anaesthesia in the adult patient. Br. J. Anaesth. 2008;100(1):8-16. doi: 10.1093/bja/aem342.
2. Cao JP, Miao XY, Liu J, Shi XY. An evaluation of intrathecal bupivacaine combined with intrathecal or intravenous clonidine in children undergoing orthopedic surgery: a randomized double-blinded study. Pediatric Anesthesia. 2011;21:399-405. doi:10.1111/j.1460-9592.2011.03543.x.
3. Gupta R, Verma R, Bogra J, Kohli M, Raman R, Kushwaha JK. A Comparative study of intrathecal dexmedetomidine and fentanyl as adjuvants to Bupivacaine**.** J Anaesthesiol Clin Pharmacol. 2011 Jul-Sep;27(3):339–43. doi: 10.4103/0970-9185.83678.
4. Gupta M, Shailaja S, Hegde KS. Comparison of Intrathecal Dexmedetomidine with Buprenorphine as Adjuvant to Bupivacaine in spinal Anaesthesia.

Journal of Clinical and Diagnostic Research. 2014 Feb;8(2):114-17. DOI: 10.7860/JCDR:2014/7883.402.

5. Mahendru V, Tewari A, Katyal S, Grewal A, Singh MR, Katyal R. A comparison of intrathecal dexmedetomidine, clonidine, and fentanyl as adjuvants to hyperbaric bupivacaine for lower limb surgery: A double blind controlled study. J AnaesthesiolClinPharmacol. 2013 Oct-Dec;29(4): 496-502. doi: 10.4103/0970-9185.119151.
6. Gertler R, Brown HC, Mitchell DH, Silvius EN. Dexmedetomidine: a novel sedative-analgesic agent. Proc (Bayl Univ Med Cent). 2001 Jan;14(1):13-21.
7. Naaz S and Ozair E. Dexmedetomidine in Current Anaesthesia Practice- A Review. J Clin Diagn Res. 2014 Oct;8(10):GE01–GE04.
8. Sachan P, Kumar N, Sharma JP. Intra thecal clonidine with hyperbaric bupivacaine .Indian J Anaesth. 2014 May-Jun;58(3):287–92
9. Greene NM. Distribution of local anesthetic solutions within the subarachnoid space. Anesthesia and Analgesia. 1985;64:715–30.
10. Abdelhamid and El-lakany. Intrathecal dexmedetomidine: Useful or not? J AnesthClin Res 2013;4:9.
11. Bromage PR. Philadelphia: WB Saunders;1978:144.
12. Marino PL, Sutin KM. The ICU Book. Sedation in ICU. Table 49.3.

Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(1) (Part - II): 323-332
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.45

A Comparisoin of Fentanyl Citrate and Magnesium Sulphate as Adjuvants to 0.5% heavy Bupivacaine in Spinal Anaesthesia

Rajola Raghu[1], Pacharla Indira[2], Vanaja[3]

[1,2]Associate Professor, [3]PG Studnet, Department of Anesthesiology and Critical Care, Osmania Medical College, Hyderabad, Telangana 500095, India.

Abstract

Spinal anaesthesia is preferred regional anaesthesia technique in lower abdominal surgeries. Advantages are conscious and spontaneously breathing patient [25], good muscle relaxation, cost effectiveness and adjuvants injected intrathecally prolong the anaesthetic effects [26,27]. *Aim of the study:* To compare Fentanyl Citrate and Magnesium sulfate as adjuvants to 3 ml of 0.5% bupivacaine in infraumbilical surgeries under spinal anaesthesia, about onset and duration of sensory and motor block, intraoperative hemodynamics, postoperative pain and side effects. *Materials & Methods:* After Institutional ethics committee approval, a double-blinded comparative study was conducted in 100 patients at Osmania General hospital during 2014-2017. Patients were divided into two groups of 50 no.'s each Group F- 3 ml 0.5% Heavy Bupivacaine & Fentanyl citrate 25 mcg, Group M –3 ml 0.5% Heavy Bupivacaine & $MgSO_4$ 100 mg were deposited intrathecally. Intraoperatively Sensory and Motor block onset and duration, HR, SBP, DBP & MAP, SpO_2, side effects were assessed. *Results:* In group M– onset of sensory and motor block is significantly prolonged , duration of analgesia, motor block is comparable to group F and patients in group M were hemodynamically stable perioperatively, and at end of 24 hrs postoperatively VAS score was ≥ 3 at indicates a quality post operative analgesia. *Conclusion:* Fentanyl citrate as adjuvant to 0.5% heavy bupivacaine effectively augmented quality of spinal anaesthesia; its advantages are limited by incidence of side effects. $MgSO_4$ 100 mg provides excellent perioperative analgesia and stable hemodynamics and is an attractive non-opioid adjuvant alternative to fentanyl.

Keywords: Adjuvants; Local anaesthetics; Magnesium sulfate; NMDA receptors; Opioids; Spinal anaesthesia.

How to cite this article:

Rajola Raghu, Pacharla Indira, Vanaja. A Comparisoin of Fentanyl Citrate and Magnesium Sulphate as Adjuvants to 0.5% heavy Bupivacaine in Spinal Anaesthesia. Indian J Anesth Analg. 2019;6(1):323-332.

Introduction

Anaesthesiologists in present day practice are also involved in effective post-operative pain management. Spinal anaesthesia is choice of anaesthesia technique in infraumbilical surgeries as it is safe and faster onset of surgical anaesthesia, provides excellent operating conditions and is economical [30]. Adjuvants [32,33] added to local anaesthe -tics act synergistically to enhance quality of spinal anaesthesia i.e., prolonged duration of sensory and motor block and effectiveness of spinal analgesia thus eliminating intra and post-operative pain [38,40]. Local anaesthetic adjuvants include

Corresponding Author: Pacharla Indira, Associate Professor, Department of Anesthesiology and Critical Care, Osmania Medical College, Hyderabad, Telangana 500095, India.

E-mail: dudyalaindira@yahoo.com

Received on 12.11.2018, **Accepted on** 03.12.2018

a wide array of drugs with different mechanisms of action eg., opioids, epinephrine, alpha-2 adren -ergic agonists, steroids, anti-inflammatory drugs, midazolam, ketamine, magnesium sulfate and neostigmine. The advantage of combining two types of agents is explained by different analgesic properties and their ability to block pain at two different sites. Opioids specifically bind and activate opiate receptors in substantia gelatinosa produce analgesia and by systemic absorption whereas local anaesthetics provide analgesia by blocking impulse transmission at nerve roots and dorsal root ganglia. Intrathecal opioids enhance sensory and motor block [45] and potentiate anti-nociception by G protien coupled receptor mechanisms and hyperpolarisation of afferent sensory neurons. Buprenorphine, Fentanyl, Sufentanyl and Afentanil [49,50] are commonly used opioid adjuvants. The dose, lipophilicity and acid-base milieu of site of drug deposition determine extent and efficacy of block [54]. Fentanyl citrate a lipophilic synthetic phenylpiperidine, μ- mu, κ-*kappa* receptor agonist, is used intrathecally in dose range of 10-25 μg has rapid onset of action strongly binds to plasma proteins, potentiates afferent sensory block in terms of onset, duration and extent of analgesia. Its effects are limited by incidence of hemodynamic instability and side effects -respiratory depression, ponv, vomiting and pruritus [29] etc.

NMDA (N-Methyl-D Aspartate) receptor channels are ligand-gated ion channels involved in pain processing, generate slow excitatory postsynaptic currents at glutaminergic synapses. A sustained NMDA receptor activation promotes intracellular signaling that results in long-term synaptic plasticity, wind-up phenomenon and central sensitization. These events determine duration and intensity of postoperative pain. Mg^{2+} and Ketamine prevent central sensitization and reduce postoperative analgesic requirements [58,59,60–61]. Mg^{2+} has antinociceptive effects by a non-competitive NMDA receptor antagonism in spinal cord [79] and its effects are based on, regulation of calcium influx [1]. Intrathecal Mg^{2+} 50 mg [2,3] decreased postoperative analgesic [4] requirements by almost 50%. Mg^{2+} may have a pre-emptive analgesic action and Epidural Mg and bupivacaine decrease pain scores and analgesic requirements for up to 72 hrs [5] without any increase in systemic side effects [6]. Although $MgSO_4$ prolongs spinal anaesthesia, it may fail to reduce bupivacaine dose requirement [8]. various options are being extensively evaluated as alternative to opioids.

Role of Magnesium in Anaesthesia

Magnesium an intrinsic component of many adenosine 5'-triphosphatases, acts as an endogenous calcium antagonist by noncompetitive inhibition of inositol triphosphate-gated Ca^{2+} channels [1,4] i.e., 'natural physiological calcium antagonism'. It is an endogenous regulator of several electrolytes [3], has modulatory effects on Na, K currents and influence membrane potential [5,6]. Its antinociceptive effects are due to NMDA glutamate receptor antagonism [7-10] and inhibition of catecholamine release. It was observed during anaesthesia serum Mg^{2+} conc. decrease and return to normal 1-3 days postoperatively [12]. Mg^{2+} has potential benefits in anaesthesia [3] and is proposed as anaesthetic, along with volatile anaesthetic agents has super additive effect at central NMDA-aspartate receptors, inhibit glutamate/glycine signaling function [24] and decrease MAC, enhance analgesia and muscle relaxation and improves patient outcomes. Many authors have studied role of $MgSO_4$ as adjuvant for providing intra and postoperative analgesia [10,1,23]. Tramer MR et al. [1]., performed a randomized, double blind study to assess effect of Mg as physiologic NMDA antagonist on analgesic requirements, pain and quality of sleep in postoperative period. Sakuraba et al. [15]., magnesium reduces catecholamine release during intubation, decreases succinylcholine induced fasciculation and may prevent hyperkalemia [14,16]. Turan et al. [18] Mg^{2+} added to lidocaine has beneficial effects in terms of improved quality of IVRA (Bier block), shorter onset times of sensory and motor blocks and better postoperative analgesia. It can be an useful analgesic adjunct in TIVA (Seyhan et al.) reduces propofol, atracurium and postoperative morphine consumption in gynecologic surgeries and concluded that it improves quality of postoperative analgesia and decreases PONV [19], due to lower consumption of volatile anesthetics (sevoflurane) [2]. Arcioni et al. [20] investigated synergistic interactions between intrathecal administration of magnesium sulfate and anaesthetics in terms of postoperative analgesia. Mg^{2+} reduces propofol, rocuronium and fentanyl in spinal surgical patients Gupta et al., [22], its use intraoperatively may decrease remifentanil-induced hyperalgesia. Mg^{2+} is effective in treatment of intra and post-operative pain an important component of postoperative recovery as it serves to blunt autonomic, somatic and endocrine reflexes with a resultant potential decrease in perioperative morbidity. Bupivacaine is most commonly used amide local anaesthetic in spinal anaesthesia, it is a white crystalline powder soluble inwater, with pH

of 5.2 and sp.gravity of 1.021 is available as 0.5% hyperbaric solution in 8% dextrosefor intrathecal use.

Aim & Objectives of the Study

To study and compare effects of Fentanyl citrate and Magnesium sulphate as adjuvant to intrathecal 0.5% heavy bupivacaine in 100 patients posted for infraumbilical surgeries, during study the following spinal anaesthesia characteristics were compared between two groups.

1. Onset and duration of Sensory Analgesia – Speed of onset and duration of analgesia.
2. Onset and duration of Motor Blockade – Speed of onset and duration of motor blockade.
3. Intraoperative Hempdynamic changes, Sedation and side effects.
4. Post operative pain assessed by Visual Analog Scale (VAS).

Materials and Methods

After Institutional Ethics Committee approval study was carried out at Govt. Maternity Hospital and Osmania General Hospital during 2014-2017, 100 randomly selected patients in age group of 18-55 yrs belonging to ASA I & II of both sex were included in study, patients were posted for infraumbilical surgeries (Ovarian cystectomy, Hysterecomy, Sac Eversion, Inguinal hernioraphy, Appendectomy, Cystolithotomy and Ureterolithotomy) under spinal anaesthesia. Pre-anaesthetic assessment done to screen and evaluate major systemic illnesses, informed consent was obtained from all patients include in study, they were explained about spinal anaesthesia procedure and educated about using *'visual analog scale'*. Patients were randomized into 2 groups based on adjuvant drug received intrathecally.

(i). Group F (n=50) -3 ml 0.5% heavy Bupivacaine + Fentanyl 25 µgm.

(ii). Group M (n=50) -3 ml 0.5% heavy Bupivacaine 0.5% +100 mg $MgSO_4$.

Patients were fasting overnight and pre-medication included tab. alprazolam 0.5 mg at bed time, tab. rantidine 150 mg at bed time and morning before surgery. On day of surgery, anaesthesia equipment checked and emergency drugs were kept ready, on arrival of patient at OR multiparameter monitor (Philips Suresign VM8) was connected and baseline vitals were recorded, 18G i.v. access secured on left forearm and all patients pre-loaded 10 ml/kg of RL15 mins prior to surgery.

Inclusion Criteria

(i) ASA physical status I & II

(ii) Age 18 to 60 yrs

Exclusion Criteria

(i) ASA Gr. III & IV

(ii) Infection at site of injection

(iii) Coagulopathy

(iv) H/o Local Anaesthetic sensitivity

Under aseptic precautions all patients received spinal anaesthesia in right lateral position at L_3-L_4 interspinous space with 26G Quincke Babcock short bevel spinal needle, after obtaining clear CSF flow with needle bevel directed cephalad, local anaesthetic and adjuvant drugs were deposited intrathecally over a period of 10 seconds. Intraoperatively, following spinal anaesthesia characters were recorded and entered into data sheet for statistical analysis.

(i) Time of onset of sensory block of T_8 level using pin prick method.

(ii) Time of onset of motor block - Bromage scale 3 assesed by Modified Bromage scale.

Modified Bromage Scale for Assesing Motor Block
Bromage 0 – Able to move hip, knee and ankle.
Bromage 1 – Unable to move hip, able to move knees and ankle.
Bromage 2 – Unable to move hip, knees but able to move ankle.
Bromage 3 – Unable to move hip, knee and ankle.

(iii) Duration of Analgesia.

(iv) Duration of motor block.

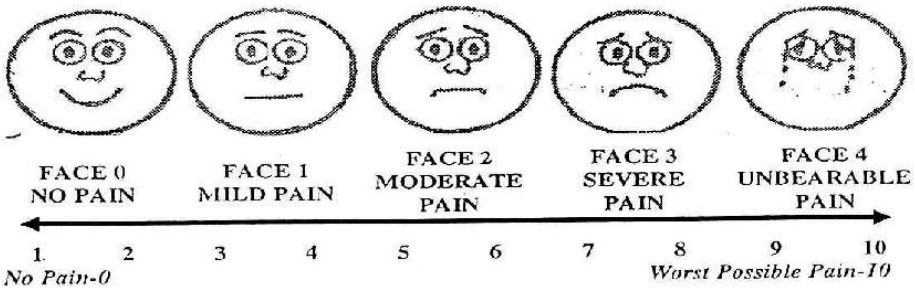
(v) Intraoperative Hemodynamics-HR, NIBP (SBP, DBP & MAP) & SpO_2 recorded every 5 mins for first 50 mins and every 10 mins till end of surgery.

(vi) Post operative sedation assessed by "*Modified Ramsay Sedation Score'* and side effects.

(vii) Postoperative pain assessed by "*Visual Analogue Scale.*"

Modified Ramsay Sedation Scale		
1	=	Agitated, restless
2	=	Cooperative, tranquil
3	=	Responds to verbal commands while sleeping
4	=	Brisk response to glabellar tap or loud noise while sleeping
5	=	Sluggish response to glabellar tap or loud noise while sleeping
6	=	No response to glabellar tap or loud noise while sleeping

Visual Analog Scale

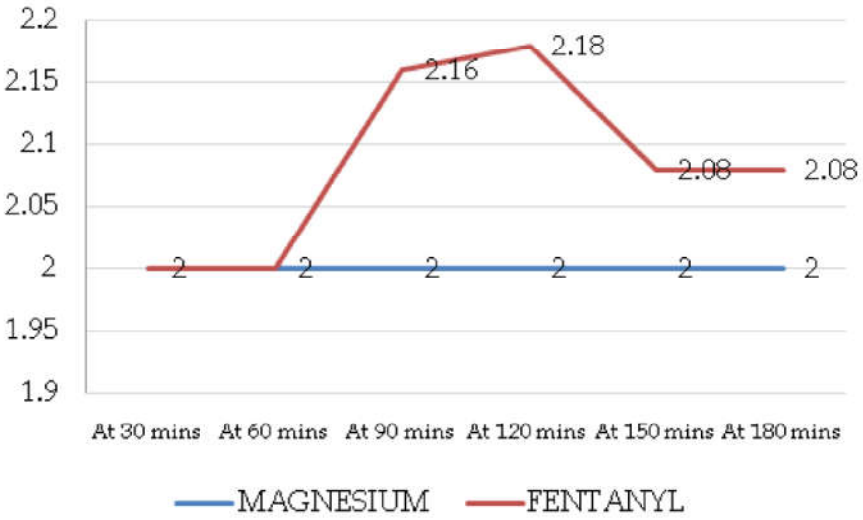


Postoperatively patients marks line on VAS to indicate pain intensity, supplemental analgesia was given for VAS score > 3 and time for analgesia supplementation was noted. Intra-operatively hypotension defined as fall in blood pressure of >20% fall from baseline MAP and treated with 0.9% NS 200 ml bolus infusion and 6 mg ephedrine i.v. Bradycardia HR<50 beats per minute was treated with 0.5 mg atropine iv. Respiratory depression defined as RR< 9 breaths/min, SpO_2 < 90% on room air. Post operatively time for 2 segement regression of sensory block and motor block to reach Bromage scale 3 to 0 were also noted.

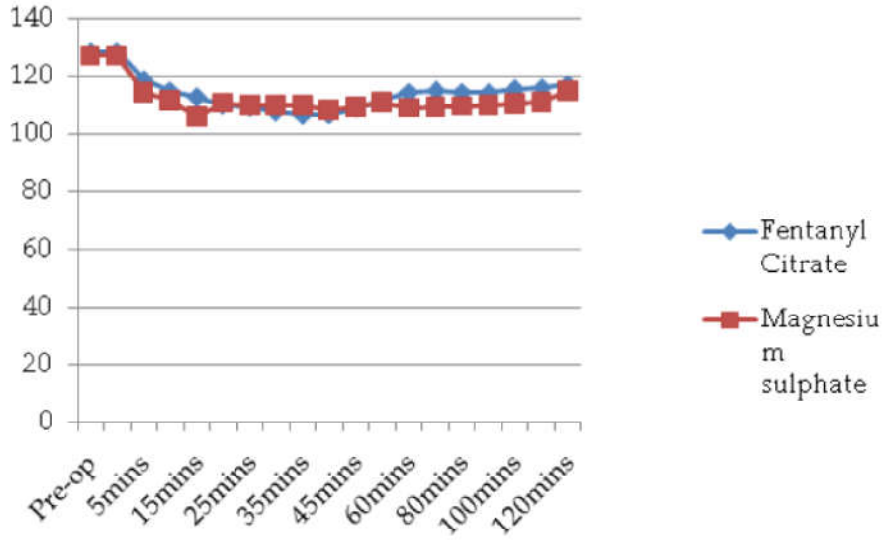
Observations and Results

Table 1: Spinal Anaesthesia Characteristics

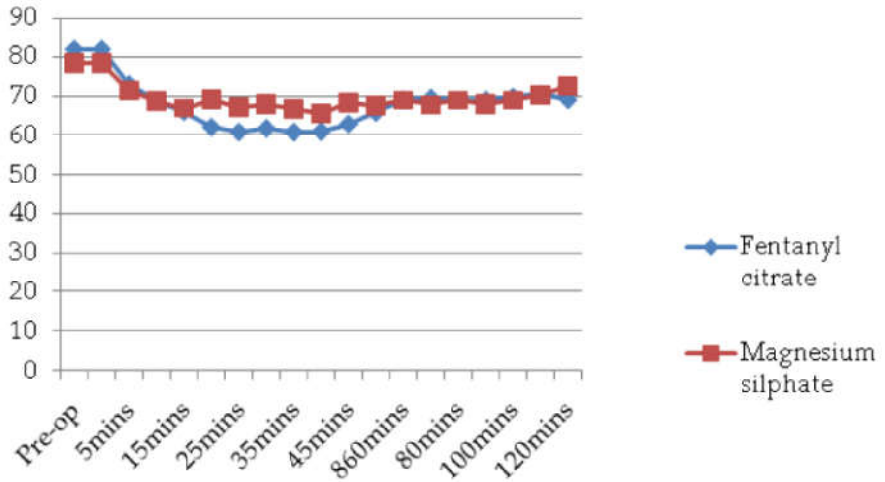
	Group F (n=50)	Group M (n=50)	'p' value
Maximum sensory level attained (n[%])			
T4	18/50(33%)	6/50 (12%)	0.042
T6	22/50	24/50	0,042
Onset to T8	2.280 + 0.50	5.63 + 0.94	0.001
Duration of Analgesia	427±46.86	365.0 + 45.99	0.001 (S)
Onset of Motor block (Modified Bromage Scale 3)	3.95 + 5.23	6.420 + 0.69	0.01
Duration of Motor block	323.92 + 48.64	278.20 + 36.67	0.001 (S)
Post-op VAS			
Post-op 2nd hours	1.04+-0.19	1.18+-0.4	0.0001(HS)
Post-op 6 hours	2.3 ±0.78	3.06±1.008	0.000 (S)
Post-op 12 hours	3.2±0.69	3.66±0.71	0.000 (S)
Post-op 24 hours	3.32±0.61	3.68±0.96	0.02(S)
First pain	427.24 + 46.86	365.00 + 45.99	0.000 (HS)
Post operative sedation (at 2 hrs)	2.18 ± 0.38	2	0.001(S)



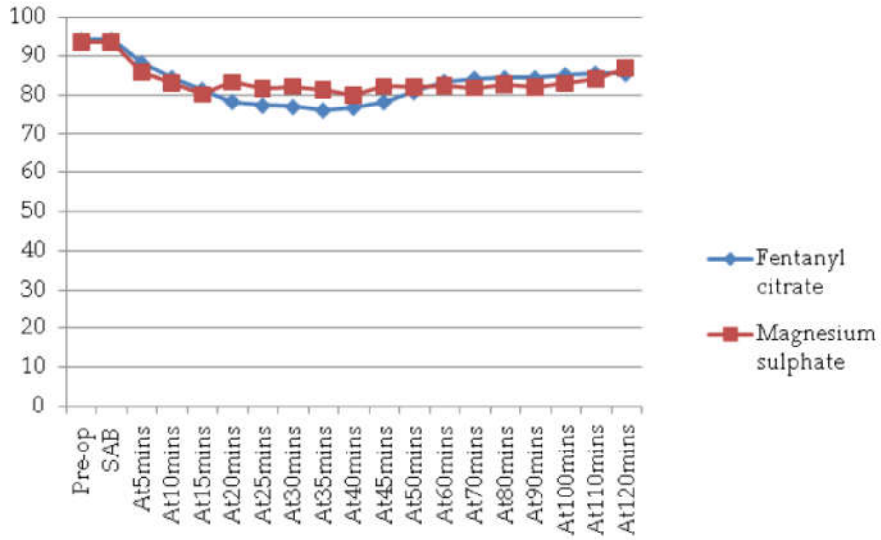
Graph 1: Modified Ramsay Sedation Score



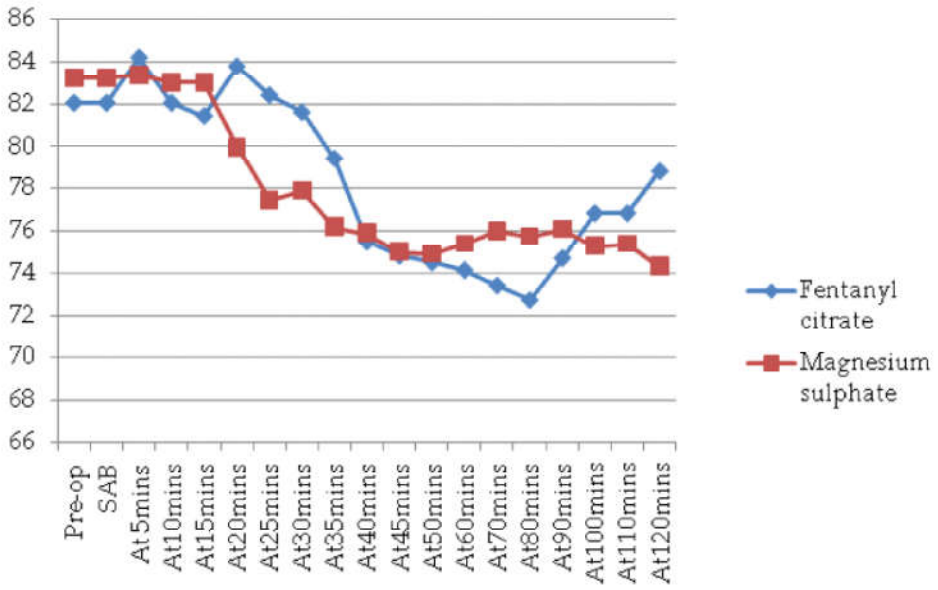
Graph 2: Changes in Systolic Blood Pressure



Graph 3: Changes in Diastolic Blood Pressure



Graph 4: Changes in Mean Arterial Pressure



Graph 5: Changes in Heart rate

Table 2: Side effects of adjuvant drugs in both groups

	Group F, Fentanyl (n=50) (n[%])	Group M, MgSO4 (n=50) (n[%])
No side effects	30 (60%)	42 (84%)
Bradycardia	0	8 (16%)
Hypotension	14 (28%)	0
Nausea	2 (4%)	0
Pruritis	3 (6%)	0
Vomiting	1 (2%)	0

Chi square = 25.0, df = 5, P value = 0.001 (S)

Statistical Methods [47,48]

Descriptive statistical analysis was carried out; results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements as percentage (%). Significancies assessed at 5% level of significance. Statistical analysis was done by applying Chi-Square test, Anova test and Students 't' test and p value determined, $p > 0.05$-not significant, $p < 0.05$ is significant, $p < 0.001$is highly significant.

Discussion

The aim of post operative pain relief is provision of subjective comfort and inhibition of surgical trauma induced nociceptive impulses, neuroendocrine responses and facilitate early functional recovery. Central sensitization is the mechanisms implicated in persistence of postoperative pain, which is dependent on activation of dorsal horn NMDA receptors by excitatory amino acid transmitters - aspartate and glutamate. A continuous search is on for newer methods to augment quality of spinal anaesthesia and prolong duration of analgesia, adding adjuvants to local anaesthetics deposited intrathecally is a method gaining popularity, is said to eliminate intra and postoperative pain. Opioids are mainstay of perioperative pain management have a dose dependent effect on duration of postoperative analgesia and are associated with significant side effects. Fentanyl has faster onset of analgesia due to its lipophilic properties and provides better intra and early post operative pain relief but has disadvantages - hemodynamic instability and systemic side-effects. NMDA antagonists have a synergistic interaction with local anaesthetics and prolong postoperative analgesia [75,76]. Study by Dayioglu et al. [74] proved addition of Mg^{2+} to local anesthetic increases duration of spinal analgesia [60,61].

Opioids use is said to be associated with immunomodulation, inhibition of pro-inflammatory cytokines, induction of long term hyperalgesia, neuroplastic changes in CNS, increase NMDA receptor activity resulting in opioid tolerance. In *vitro* studies have shown that Mg^{2+} significantly inhibited endotoxin-induced up-regulation of inflammatory molecules and NF-kB, by inhibiting L-type calcium channels. Ketamine and Mg^{2+} as NMDA receptor antagonist prevent occurrence and recurrence of all opioid induced phenomena. Koining reported intravenous Mg^{2+} significantly decreases fentanyl consumption in peri and post-operative periods, may act as an analgesic adjuvant (McCartney et al., 2004).

Khalili GI, Janghorbani M et al. [56,57]., 100 mg of $MgSO_4$ added to 15 mg of 0.5% heavy bupivacaine hcl with out opioids significantly prolonged duration of sensory block and onset of spinal anaesthesia.,

Sudharshan Kumar et al. [58] concluded intrathecal Magnesium sulfate (100 mg) as an adjuvant prolongs duration of analgesia and decreases demand for rescue analgesics than 50 mg.[34] $MgSO_4$ @100 mg dose or Fentanyl 25 µg as adjuvants to intrathecal 0.5% heavy bupivacaine significantly prolongs duration of analgesia, $MgSO_4$ provides better haemodynamic stability with fewer side effects., Sarika Katiyar, Chhavi Dwivedi et al. [59].

Beigomkhezri et al. [60] concluded $MgSO_4$ (50 mg) along with 0.5% heavy bupivacaine significantly prolonged onset of both sensory and motor blockade compared with fentanyl. Rajesh vasure et al. [62]., concluded intrathecal bupivacaine along with 50mg $MgSO_4$ results in significant prolongation of duration of analgesia with a more stable hemodynamic profile and lesser side effect and onset of sensory block was significantly delayed. Syed aliaasim et al concluded, (100 mg) magnesium sulphate or (25 µg) fentanyl as adjuvants to 0.5% heavy bupivacaine to spinal anaesthesia. With magnesium, in Group BM there was slower ascent of drug, probably due to change in baricity of drug. Analysis of intra-operative haemodynamics showed that the incidence of hypotension and bradycardia was more in fentanyl group as compared to magnesium group [61].

Very few studies are available describing pros and cons regarding each adjuvant, present clinical study was undertaken on basis of evidence shown above, it is suggested that magnesium may be a useful adjuvant to opioids for spinal anesthesia [62]. Intraoperatively spinal anaesthesia characteristics and hemodynamic parameters have been observed, compared and analysed between fentanyl citrate and magnesium sulphate groups in terms of efficacy and safety as intrathecal adjuvants.

In present study, onset of T_8 level sensory block with fentanyl (25mcg) is faster 2.280±0.50 mins and $MgSO_4$ (100 mg) is 5.63±0.94 mins, the onset time statistically significant with 'p' value of 0.001. The maximum height of sensory level T_4 was achieved in 36% of patients in group F(n=18) and 12% of patients in group M (n=6) with 'p' value of 0.042 is significant statistically. Motor block onset time- bromage scale 3 in group F-3.9 mins±0.23 and group M-6.4 mins±0.69 statistically significant with 'p' value of 0.01.

The delay in onset results in our study are in accordance with studies by Rajesh vasure et al., a T4 sensory level with $MgSO_4$ 50 mg a was achieved in 4.45 mins, fentanyl 25 mcg in 1.62 mins. In study by Beigom et al., sensory level of T10 was achieved in 5.86 mins ($MgSO_4$ 50 mg), 1.46 mins (fentanyl 25 µg) it is evident from above studies that $MgSO_4$ delayed the onset of sensory block compared to fentanyl. It is evident that $MgSO_4$ delayed onset, this could be explained that slower ascent of drug is probably due to changes in baricity of spinal drug [59].

The duration of analgesia in our study was - group F (fentanyl 25 mcg) 427±46.86 mins group M (100 mg) -365±45.99 mins, difference in duration of analgesia is statistically significant with 'p' value of 0.001(S), duration of motor block in group F - 323.92 ±48.64 mins and group M - 278.20±36.67 mins, the difference between two groups was statistically significant with 'p' value of 0.001 (S). In this study we found fentanyl (25 µg) as adjuvant prolonged duration of analgesia -427.24±46.86 mins in comparision with $MgSO_4$ -365.0±45.99 mins, Mg^{2+} shorter duration of analgesia may be due to increase in bupivacaine's metabolism by activation of cytochrome P 450.

Khalili G, Janghorbani M et al. study duration of analgesia was significantly longer with 100 mg Mg^{2+} is 178 mins compared to control group (normal saline) 167.4 mins. In Sarika Katiyar, Chhavi Dwivedi et al. study duration of analgesia was significantly longer 374.37 mins with 25 µg fentanyl compared to 100 mg $MgSO_4$ 328.13 mins. Syed aliaasim et al., duration of analgesia with 25 µg fentanyl -377 mins as compared to $MgSO_4$, 100 mg 326 mins. Rajesh vasure et al. duration of analgesia was significantly longer with Fentanyl 25 µg -238 mins as compared to spinal $MgSO_4$, 50 mg -164 mins. In Beigom et al., study duration of analgesia with intrathecal fentanyl 25 µg -183 mins as compared to intrathecal $MgSO_4$ (50 mg) -133 mins, duration of motor block $MgSO_4$-118 mins and Fentanyl-171 mins. In Sarika Katiyar, Chhavi Dwivedi et al. duration of motor block with 100 mg $MgSO_4$ is 228 mins as compared to 291 mins with 25µ fentanyl. It is observed in above studies higher doses of $MgSO_4$ prolongs duration of analgesia.

In present study 100mg of magnesium sulphate and fentanyl 25 µg were taken as adjuvants to 0.5% heavy bupivacaine to study effects on spinal anaesthesia, the findings were fentanyl prolongs duration of analgesia and duration of motor block compared to $MgSO_4$, the hemodynamic parameters were compared between two groups it was observed that incidence of hypotension was

28% of patients in group F and none in group M which was statistically significant with 'p' value of 0.001, results were similar to observations made in the studies by Syed aliaasim et al. (19% decrease) and Sarika Katiyar, Chhavi Dwivedi et al. (20% decrease). The absence of hypotension in group M may be attributable to gradual onset of sympathetic blockade, bradycardia was found in 16% of patients in Mg^{2+} group, similar to observations made in Hemalatha et al study.

The incidence of side effects were compared, patients in group F experienced nausea (n= 2, 4%), vomiting (n=1, 2%) and pruritis (n=3, 6%) in group M- no ponv, the observations were similar lines to study by Rajesh vasure et al. The absence of nausea, vomiting and shivering in group M ($MgSO_4$), could be explained due to propable inhibitory action on nausea and vomiting and it decreases the incidence of shivering . The post-operative pain was measured by VAS scale, group F had lower VAS scores at 2, 3, 4, 6, 12, 24 hrs, the time taken for first request of analgesia with fentanyl group - 427.24±46.86 mins, magnesium group- 365.00±45.99 mins which is statistically significant ('p' value 0.000). Rajesh vasure et al., study the time taken for first request of analgesia in group F (fentanyl 25 mcg) was 238 mins and in group M ($MgSO_4$ 50 mg) was 164 mins. In Beigom et al study time for the first request of analgesia with fentanyl -699 mins compared with $MgSO_4$ (50 mg)-318 mins. In Sarika Katiyar, Chhavi Dwivedi et al. study the time taken for first request of analgesia with fentanyl was 374 mins and $mgso_4$ 100 mg was 328 mins.

It is observed that magnesium failed to prolong the time to first analgesic requirement possible cause is vasodilatory action of $MgSO_4$ which vasodilates tissues around injection site, will eventually accelerates systemic uptake of local anesthetics and also it activates cytochrome p 450 increase bupivacaine hydroxylation and rapid elimination of bupivacaine. The dose requirement of rescue analgesic (diclofenac sodium) in group F was 82.5±6 mg when compared to group M - 165 ±22.5 mg the difference is statistically significant. The findings in our study reinforce the role of magnesium sulfate, an NMDA antagonist, as an effective spinal adjuvant to prevent induction of central sensitization and prolongs duration of analgesia and is an effective alternative to opioids.

Limitations

1. Single doses of drugs have been studied.
2. Plain bupivacaine has not been used in the study.
3. Plasma concentration in specific reference to $MgSO_4$ has not been measured.
4. Other surgeries can be included only infraumbilical surgeries are included.
5. Comparison of $MgSO_4$ and fentanyl can be done in other regional techniques.
6. Sample size is small, it cannot be concluded the results of present study are definitive.
7. More studies are required to conclude results.

Further recommendations

1. There is scope for further studies related to this topic.
2. Different doses of magnesium can be compared and studied.
3. Continuous intrathecal infusion of magnesium can be studied.
4. Synergism of combination of magnesium with other drugs to be evaluated.
5. Use of intrathecal magnesium along with iv or by wound infiltration can be done to study effect of blocking both peripheral and central sensitization, to evaluate its optimal role in reducing postoperative analgesic requirements.

Conclusion

Fentanyl 25 µg and $MgSO_4$ 100 mg as adjuvants to 0.5% heavy bupivacaine prolongs duration of spinal anaesthesia. Fentanyl has faster onset and better quality of analgesia in terms of patient satisfaction its advantages are limited by side effects, magnesium sulphate provides excellent quality of postoperative analgesia and no side effects and is an attractive alternate non-opioid intrathecal adjuvant.

References

1. Tramer MR, Schneider J, Marti RA, Rifat K. Role of magnesium sulfate in postoperative analgesia. Anesthesiology. 1996;84:340–47. [PubMed].
2. Do SH. Usefulness of magnesium sulfate in the field of anesthesia and pain medicine. Anesth Pain Med. 2008;3:157–161.
3. Dube L, Granry JC. The therapeutic use of magnesium in anesthesiology, intensive care and emergency medicine: a review. Can J Anaesth. 2003; 50:732–46. [PubMed].
4. Herroeder S, Schonherr ME, De Hert SG, Hollmann MW. Magnesium-essentials for anaesthesiologists.

Anaesthesiology. 2011;114:971-93.[Pubmed]

5. Morrison AP, Hunter JM, Halpern SH, Banerjee A. Effect of intrathecal magnesium in the presence or absence of local anaesthetic with and without lipophilic opioids: a systematic review and meta-analysis. Br J Anaesth. 2013;110:702–12. [PubMed]
6. Schulz-Stubner S, Wettmann G, Reyle-Hahn SM, Rossaint R. Magnesium as part of balancedgeneral anaesthesia with propofol, remifentenil and mivacurium: a double- blind prospective study in 50 patients. European Journal of Anaesthesiology. 2001;18:723-9.
7. Ko SH, Lim HR, Kim DC, Han YJ, Choe H, Song HS. Magnesium sulfate does not reduce postoperative analgesic requirements. Anesthesiology. 2001;95(3):640-6.
8. Hollmann MW, Liu HT, Hoenemann CW, Liu WH, Durieux ME. Modulation of NMDA receptor function by ketamine and magnesium. Part II: interactions with volatile anesthetics. Anesth Analg 2001;92(5):1182-91.
9. Liu HT, Hollmann MW, Liu WH, Hoenemann CW, Durieux ME. Modulation of NMDA receptor function by ketamine and magnesium: Part I. Anesth Analg. 2001;92(5):1173-81.
10. Kara H, Sahin N, Ulusan V, Aydogdu T. Magnesium infusion reduces perioperative pain. European Journal of Anaesthesiology. 2002;19:52-6.
11. Okuda T, Kura M, Hatsuoka K, Izumi T, Koga Y. Changes in ionized magnesium concentrations during general anesthesia. Masui. 1999;48(2):136-40.
12. Turan A, Memiş D, Karamanlioğlu B, Güler T, Pamukçu Z. Intravenous regional anesthesia using lidocaine and magnesium. Anesth Analg. 2005; 100:1189–92. [PubMed].
13. Ryu JH, Kang MH, Park KS, Do SH. Effects of magnesium sulphate on intraoperative anaesthetic requirements and postoperative analgesia in gynaecology patients receiving total intravenous anaesthesia. Br J Anaesth. 2008;100:397–403. [PubMed].
14. Apfel CC, Kranke P, Katz MH, Goepfert C, Papenfuss T, Rauch S, et al. Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting: a randomized controlled trial of factorial design. Br J Anaesth. 2002;88:659–68. [PubMed].
15. Seyhan TO, Tugrul M, Sungur MO, Kayacan S, Telci L, Pembeci K, et al. Effects of three different dose regimens of magnesium on propofol requirements, haemodynamic variables and postoperative pain relief in gynaecological surgery. Br J Anaesth. 2006;96:247–52. [PubMed].
16. Arcioni R, Palmisani S, Tigano S, Santorsola C, Sauli V, Romano S, et al. Combined intrathecal and epidural magnesium sulfate supplementation of spinal anesthesia to reduce post-operative analgesic requirements: a prospective, randomized, double-blind, controlled trial in patients undergoing major orthopedic surgery. Acta Anaesthesiol Scand. 2007;51:482–89. [PubMed].
17. Gupta K, Vohra V, Sood J. The role of magnesium as an adjuvant during general anaesthesia. Anaesthesia. 2006;61:1058–63. [PubMed].
18. Nastou H, Sarros G, Palta M, Nastos A, Sarrou V, Anastassopoulou J. Fluctuations in serum magnesium levels during total intravenous anaesthesia with propofol. Magnes Res 1996;9(1):47-53.
19. NicholasM.Greene–Distribution of local anesthetic solution with in the subarachnoid space, Anaes Analg 1985;64:715-30.
20. B.R. Raymond Fink—Mechanisms of differential axial blockade in epidural and subarachnoid anaesthesia, Anaesthesiology. 1989;70:815-58.
21. Michael J Cousins and Laurence E Mather – Intrathecal and epidural administration of Opioids, Anesthesiology. 1984(61):276-10.
22. Mark A Chaney. Side effects of intrathecal and epidural opioids, Can. J. Anesthesia. 1995;42(10):891-903.
23. Robert. K. Stoelting: Pharmacology and Physiology in Anaestheticpractice, 3rd Edition.
24. A. Gupta K. Axelsson SE. Thornetal—Low dose Bupivacaine plus Fentanyl for spinal anaesthesia during ambulatory inguinal herniorraphy: A comparison between 6 mg and 7.5 mg of bupivacaine, ActaAnaesthiol Scand. 2003;47:13-19.
25. Kararmaz. A. Kaya S, Turhanoglu. S. et al. Low dose bupivacaine Fentanyl spinal anaesthesia for transurethral prostetectomy, Anaesthesia. 2003;58(6):526-30.
26. H. Singh, J. Yang, K. Thorntonetal. Intrathecal Fentanyl prolongssensory bupivacaine spinal block. Can JAnesth. 1995;42(11):987-91.
27. Bengt Akerman, Ewa Arwestrom and Claase Post et al.,—Local anaesthetics potentiate spinal Morphine antinociception, Anesth and Analg. 1988;67:943-9.
28. R. C. Etches, A.N. Sandler and MD Daley et al. Respiratory Depression and spinal opioids, Can J Anaesth. 1989 Mar;36(2):165-85.
29. Scott S Reuben, Steven M., Dunn Karen MD. An Intrathecal Fentanyl dose-response study in lower extremity revascularization procedures, Anesthesiology. 1994:81(6):1371-75.
30. Martin Cascio, Bernard Pygon, Cathleen B et al., —Labour analgesia with intrathecal Fentanyl decreases maternal stress, CanJAnesth. 1997;44 (6):605-09.
31. Chen Wang. MB, Mihir K. Chakrabarti, James G. Whitwam et al. Specific enhancement by Fentanyl of the effects of Intrathecal Bupivacaine on nociceptive afferent but not on sympathetic efferent pathways in dogs. Anesthesiology. 1993;79:766-73.

32. BruceBen-David, Eric Solomon, et al., - Intrathecal Fentanyl with small dose dilute Bupivacaine: Better anaesthesia without prolonging recovery, AnesthAnalg. 1997;85:560-65.

33. Craig M. Palmer, Gretchen Van Maren, Wallace M. Noga- mi et al.,—Bupivacaine augments Intrathecal Fentanyl for labouranalgesia, Anesthesiology. 1999;91(1):82-89.

34. Khalili G, Janghorbani M, Sajedi P, Ahmadi G. Effects of adjunct intrathecal magnesium sulfate to bupivacaine for spinal anesthesia: A randomized double-blind trial in patients undergoing lower extremity surgery. J Anesth. 2011;25:892–7.

35. Chaudhary SK, Verma RK, Rana S, Singh J, Danesh A. Magnesium sulfate at two different doses as an adjuvant to bupivacaine in infraumblical (below knee) orthopedic surgeries under spinal anesthesia. Ain-Shams J Anaesthesiol 2016;9:416-21.

36. Katiyar S, Dwivedi C, Tipu S, Jain RK.Comparison of diferent doses of magnesium sulphate and fentanyl as adjuvants to bupivacaine for infraumbilical surgeries under subarachnoid block. Indian J Anaesth. 2015;59;471-5.

37. Marzieh-Beigom Khezri, Siamak Yaghobi, Mahsa Hajikhani, Saeid Asefzadeh. Comparison of postoperative analgesic effect of intrathecal magnesium and fentanyl added to bupivacaine in patients undergoing lower limb orthopedic surgery ActaAnaesthesiol Taiwan. 2012;50:19-24.

38. Aasim SA, Reddy S, Reddy M, et al. A comparative study of the different doses of magnesium sulphate and fentanyl as adjuvants to bupivacaine [0.5% heavy] for lower abdominal surgeries under subarachnoid block. J.Evolution Med. Dent. Sci. 2016;5(32):1735-38.

39. Vasure R, Ashahiya ID, Narang N, Bansal R. Comparison of Effect of Adding Intrathecal Magnesium Sulfate to Bupivacaine Alone and Bupivacaine-Fentanyl Combination during Lower Limb Orthopedic Surgery. Int J Sci Stud. 2016;3(10):141-46.

40. Arcioni R, Palmisani S, Tigano S, Santorsola C, Sauli V, Romanò S, et al. Combined intrathecal and epidural magnesium sulfate supplementation of spinal anesthesia to reduce postoperative analgesic requirements. ActaAnaesthesiol Scand. 2007;51:482–9.

41. Fei Xiao, Lin Liu, Wang-Ping Zhang, Xiang-Yang Chang, Yin-Fa Zhang Effect of adding magnesium sulfate to intrathecal low-dose of bupivacaine for patients with severe pre-eclampsia undergoing cesarean delivery Int J ClinExp Med. 2016;9(10):19749-56.

42. Hari Krishna Dalai, Shree Nanda, SiddharthChavali, A Clinical Comparison between Intrathecal and Intravenous Infusion of Magnesium Sulphate as an Adjuvant to Hyperbaric 0.5% Bupivacaine in Spinal Anaesthesia for Elective Infraumbilical Surgeries. Annals of International Medical and Dental Research. 2017;3(2):23-29.

43. Nath MP, Garg R, Talukdar T, Choudhary D, Chakrabarty A. To evaluate the efficacy of intrathecal magnesium sulphate for hysterectomy under subarachnoid block with bupivacaine and fentanyl: A prospective randomized double blind clinical trial. SaudiJ Anaesth. 2012;6:254-8.

44. Dayıoğlu H, Baykara ZN, Salbes A, Solak M, Toker K. Effects of adding magnesium to bupivacaine and fentanyl for spinal anesthesia in knee artroscopy. J Anesth. 2009;23:19-25.

45. Katiyar S, Dwivedi C, Tipu S, Jain RK. Comparison of different doses of magnesium sulphate and fentanyl as adjuvants to bupivacaine for infraumbilical surgeries under subarachnoid block. IJA. 2015;59:471-5.

46. Kroin JS, McCarthy RJ, Von Roenn N, et al. Magnesium sulphate potentiates morphine antinociception at the spinal level. Anesth Analg. 2000;90:913-7.

47. Liu HT, Hollmann MW, Hoenemann CW, Liu WH, Durieux ME. Modulation of NMDA receptor function by ketamine and magnesium. Part II. Anesth Analg. 2001;92:1173-81.

48. Woolf CJ, Chong MS. Preemptive analgesia-treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg. 1993;77:362.

Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(1) (Part - II): 333-340
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.46

A Prospective Study of Thoracic Epidural Anaesthesia for Upper Abdominal Surgeries

Shivananda PT[1], Shashank M[2]

[1]Associate Professor [2]Senior Resident, Dept. of Anaesthesia, Shivamogga Institute of Medical Sciences, Shivamogga, Karnataka 577201, India.

Abstract

Background: Upper abdominal surgeries were coneventionally done under general anaesthesia. Now a days epidural anaesthesia is being used for upper abdominal surgeries as it can be used for both intraoperative anaesthesia & postoperative analgesia thus decreasing postoperative morbidity. *Materials & methods:* 50 patients in the age group of 20 to 50 years of either sex, with ASA physical status score 1 or 2, scheduled to undergo elective upper abdominal surgeries were included in the study. Epidural catheter was inserted in T8-T9 interspace in all patients considered for the study. 10cc 0.5% bupivacaine was given in all patients. All the observations were noted down & results analysed. *Conclusion:* Thoracic epidural anaesthesia is an excellent option for upper abdominal surgeries. It provides good intraoperative anaesthesia & postoperative analgesia facilitating early recovery. It prevents the risks associated with general anesthesia. Hence, we conclude that thoracic epidural anaesthesia should be a part of the armamentarium of anaesthesiologists in upper abdominal surgeries.

Keywords: Epidural; Thoracic; Upper Abdominal Surgery.

How to cite this article:

Shivananda PT, Shashank M. A Prospective Study of Thoracic Epidural Anaesthesia for Upper Abdominal Surgeries. Indian J Anesth Analg. 2019;6(1):333-340.

Introduction

Major surgery induces profound physiological changes in the preoperative period, characterized by increase in sympathoadrenal and other neuroendocrine andalso an increased cytokine production. As epidural anaesthesia can attenuate this "stress response" to surgery, improve the quality of postoperative analgesia in comparison with systemic opioids, and hasten recovery of gut function, it been suggested that conducting surgery under epidural anaesthesia may reduce preoperative morbidity and mortality compared with general anaesthesia alone [1].

All segments of the spinal canal from base of skull to sacral hiatus are available for epidural injection and epidural analgesia can be adapted to almost any type of surgery below chin [2]. Dawkins and steel [3] reported that ideal conditions for upper abdominal surgery can be obtained by instilling the local anesthetic agents into the epidural space at the midpoint of nerve supply to the site of operation.

Thoracic epidural anaesthesia was introduced fifty years ago to provide anaesthesia to awake unintubated patients during intrathoracic surgical procedures [4]. Subsequently, thoracic epidural anaesthesia and analgesia have been utilized in the intraoperative and post operative anaesthetic

Corresponding Author: Shashank M, Senior Resident, Dept. of Anaesthesia, Shivamogga Institute of Medical Sciences, Shivamogga, Karnataka 577201, India.

E-mail: shashankm.07@gmail.com

Received on 31.10.2018, **Accepted on** 13.12.2018

management of patients undergoing thoracic and upper abdominal surgery [5-6]. Although lumbar spinal and epidural blockade are often preferred by the anesthetist, primarily because of the technically less difficult needle placement and decreased probability of dural puncture and neural injury, thoracic epidural anaesthesia provides selective blockade of the surgical site, with diminished requirement of opioids and local anaesthetics. In addition thoracic epidural anaesthesia provides pain relief and sympatholysis of such magnitude that allows patient to cough, breathe deeply, drink and mobilize which can contribute to enhanced post operative outcomes such as improved respiratory function, reduction in ileus and protein sparing [7].

The routinely followed anaesthetic technique for upper abdominal surgeries was conventional general anaesthesia. General anaesthesia has its own drawbacks especially in patients with pulmonary disease, cardiac disease, metabolic disease or patient with morbid obesity where it leads to instrumentation of airway, ventilation perfusion mismatch, and administration of depressant drugs, which can lead to intra-operative and post-operative complications.

So, we decided to do this clinical study to evaluate the usefulness of employing the thoracic segmental epidural blocks for various upper abdominal surgeries using 0.5% bupivacaine. The effectiveness of thoracic epidural anaesthesia for upper abdominal surgeries using 0.5% bupivacaine, was analysed and the following parameters were studied, time of onset of analgesia, level of blockade, quality of analgesia, degree of motor blockade, duration of analgesia, hemodynamic response to anaesthesia and surgery (HR, NIBP, $SpO_2$and RR), and intra-operative and post-operative complications.

Methods

This prospective clinical study was conducted in the Department of Anaesthesiology, at McGann Hospital, Shimoga Institute of Medical Sciences, Shivamogga by a single anaesthetist. After informed and written consent 50 patients in the age group of 20 to 50 years of either sex, with ASA physical status score 1 or 2, scheduled to undergo elective upper abdominal surgeries wereincluded in the study. Exclusion criteria were ASA grade 3 and 4, Contraindications for epidural anaesthesia like, uncooperative patients, severe haemorrhage or shock, coagulation defects, local inflammation and failed epidural or inadequate block level, for surgery.

In all patients selected for the study, a detailed history of present and past medical and surgical illnesses and medication use was taken and a detailed general physical examination, including airway assessment, spine and systemic examination was done with required blood investigations like hemogram, bleeding time, clotting time, blood grouping and Rh typing, HIV 1 and 2, and HbsAg in all patients. RBS, blood urea, serum creatinine, ECG and chest X-ray was also done depending on the requirement.

All the patients were advised to remain nil per oral after midnight and was given tab Diazepam 0.2 mg/kg orally the night before surgery. On the day of surgery and on arrival into operating room, an 18 gauge i.v. catheter was secured and the patient was preloaded with 500 ml Ringer Lactate solution over a period of 20 to 30 min. Basal vital parameter like pulse rate/heart rate, blood pressure, ECG, respiration, oxygen saturation recorded.

Procedure

The patient in sitting or lateral position with the help of an assistant, under aseptic precaution, the back will be prepared with 5% povidine iodine solution, spirit and the area was draped. The inferior angle of scapula which corresponds to T_7 spine is palpated and T_8-T_9 space located. The skin is infiltrated with 2 ml of 2% lignocaine and after 60 to 90 seconds, a Tuohy`s epidural needle,18G will be introduced along the midline in T_8 -T_9 space and advanced obliquely with 45^0 to the skin till the needle is steady in the inter-spinous ligament. The stylet is removed and a 10 cc dry glass syringe with an air column of 5 cc is attached firmly to the hub of the needle. This unit was carefully advanced with 45^0 angle and constant pressure applied on the plunger of the syringe. As long as the needle point is in the ligaments there will be relative or absolute resistance to injection but as the point emerged from the ligamentum flavum onto the epidural space resistance suddenly disappeared. After confirmation of loss of resistance in all directions, 18G epidural catheter is threaded through the epidural needle into the epidural space in cephalad direction upto about 3 to 5 cm. The epidural needle is steadily pulled out without disturbing the catheter. The catheter was well secured with plaster and patient was positioned supine for surgery. A test dose of 3 ml of 2% Lignocaine with 15 µg of epinephrine was administered after negative aspiration for blood or CSF. The patient was observed for 5 minutes to ensure that the injection is not into the subarachnoid space or epidural

vessels. Then 10 cc of 0.5% bupivacaine was injected steadily at a rate of 0.5 ml/second for all patients. Pulse, NIBP, SpO_2, ECG, and respiratory rate was recorded before the start of procedure (Baseline values) and every 5 min, 10 min, 15 min, 30 min, 45 min thereafter, till patient is shifted out from the recovery room. If bradycardia occurs at anytime (<50 beats / min), then 0.6 mg of injection atropine was given. If hypotension occurs then it is treated appropriately with i.v. fluids and vasopressors.

The parameters studied are,

1) Time of onset of analgesia in minutes - It is recorded as interval between the time of injection into the epidural space and development of loss of sensation to pin prick.

2) Quality of analgesia - This is graded as follows:

Grade I - Analgesia is complete and sedatives are administered only to relieve apprehension.

Grade II - Analgesia is incomplete, inadequate or patchy and supplementation is needed with narcotics or ketamine or N_2O/O_2/ halothane.

Grade III - Analgesia is very poor and the technique will be changed over to general anaesthesia.

3) Assessment of motor blockade - Abdominal muscle power is assessed by the rectus abdominis muscle (RAM) test.

100% Power: Able to rise from supine to sitting position with hands behind head.

80% Power: Can sit only with arms extended.

60% Power: Can lift only head and scapulae off bed.

40% Power: Can lift on shoulders off bed.

20% Power: An increase in abdominal muscle tension can be felt during effort - no other response.

Surgeon's opinion is also taken during the procedure and degree of motor blockade is graded as follows:

Grade I: Complete block - good relaxation

Grade II: Partial block - intermediate.

Grade III: No block - Poor relaxation.

4) Duration of analgesia - This is measured as the interval between onset of analgesia and regression of analgesia by 2 segments.

5) Intra operative complications - Patients are carefully monitored for any untoward effects like, hypotension, bradycardia, respiratory distress, nausea - vomiting, shivering.

Hypotension is considered when fall in systolic BP is 30% less than the baseline. Hypotension is treated with intravenous fluid administration and use of vasopressors as required. Bradycardia is considered when heart rate is less than 50 beats/ min, is treated with injection of Atropine 0.6 mg.

6) Post operative complications - All the patients are observed on the day of surgery and on the first and second post operative day to note any complications such as PDPH, Backache, nausea, vomiting, retention of urine, any signs of neurological sequelae, infection and catheter related problems (kinking, migration etc).

Results

Patients in the study had following demographic parameters, which included age, gender, height and ASA Physical status distribution (Tables 1-4).

Table 1: Demographic data

Age group (yrs)	Male	female	Total
21-30	9	11	20
31-40	7	8	15
41-50	9	6	15
Total	25	25	50
Mean ± SD	36.6±9.3	33.9±9.4	35.3±9.4

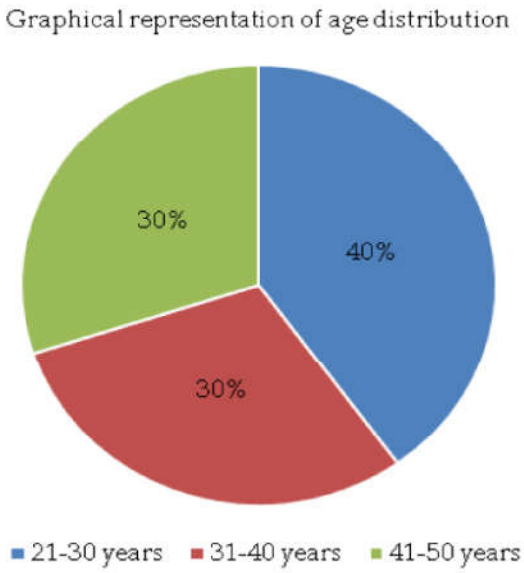


Fig. 1: Demographic data

Table 2: Height distribution

Height (cm)	Male	Female	Total
151-160	-	17	17
161-170	13	8	21
171-180	12	-	12
Total	25	25	50
Mean± SD	170.6± 3.7cm	159.3± 4.2cm	165.0± 6.9cm

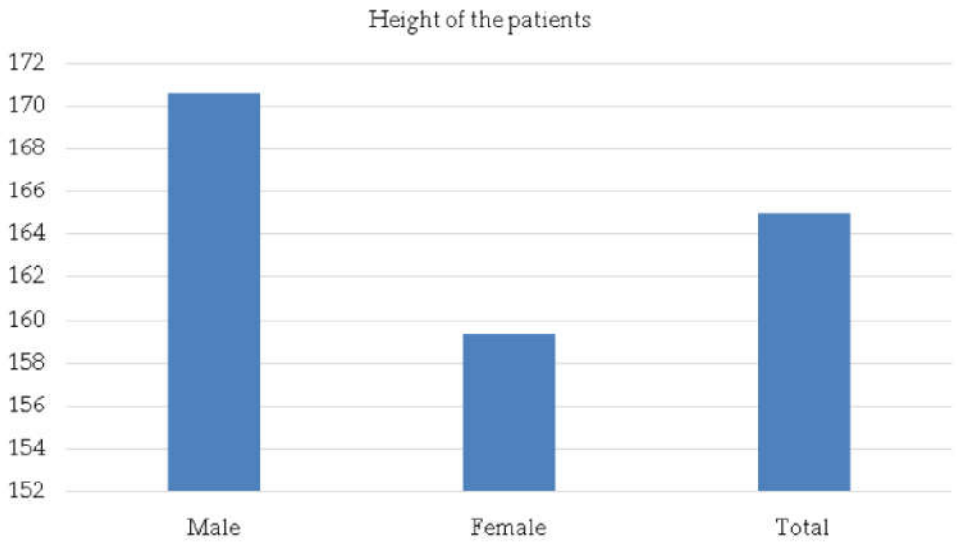


Fig. 2: Height distribution

Table 3: Types of surgical procedure

Surgical procedure	Number of cases	Percentage
Cholecystectomy	22	44
Epigastric hernia	8	16
GJ vagotomy	14	28
Hemicolectomy	2	4
Hydatid cyst liver	2	4
Pseudopancreatic cyst	2	4
Total	50	100

Table 4: ASA distribution

ASA grade	No of cases	Percentage
I	40	80
II	10	20
Total	50	100

Table 5: Onset of analgesia

Onset (In minutes)	No of cases	Percentage
15	12	24
16	9	18
17	4	8
18	11	22
19	1	2
20	8	16
22	3	6
Failure	2	4
Total	50	100

Range = 15-22 min Mean ± SD = 17.4 ± 2.1 min

The upper level of blockade for majority of the patients was T3-T4 level (Table 5).

Table 6: Upper level of blockade

Blockade level	Number of cases	Percentage
T1	5	10
T2	3	6
T3	15	30
T4	16	32
T5	8	16
T6	1	2

Table 7: Lower level of blockade

Blockade level	Number of cases	Percentage
T12	19	39.6
L1	19	39.6
L2	10	20.8

Hemodynamic parameters were as follows: systolic blood pressure and diastolic pressure were 122.4±11.3 mm Hg and 76.1±9.1 mm Hg at the beginning and at minutes 108.2±17.5 mm Hg and 72.2±9.4 mm Hg, and was 112.2±11.3 mm Hg and 78.6±6.4 mm Hg respectively. Heart rate/pulse rate and mean blood pressures of the patients is shown in the Fig. 3 and 4 (Table 6 and 7).

Table 8: Duration of analgesia

Duration(min)	No of cases
110	4
115	5
120	8
125	4
130	11
135	8
140	8

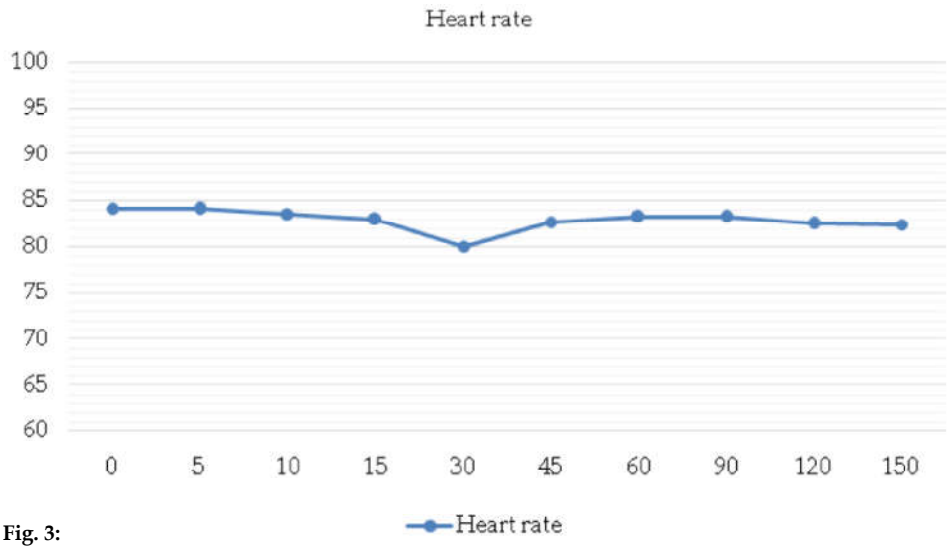


Fig. 3:

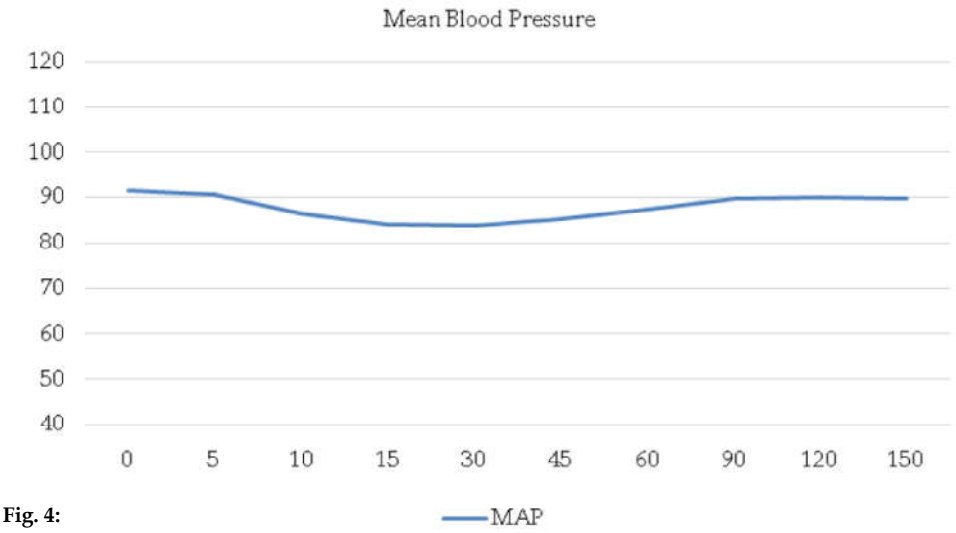


Fig. 4:

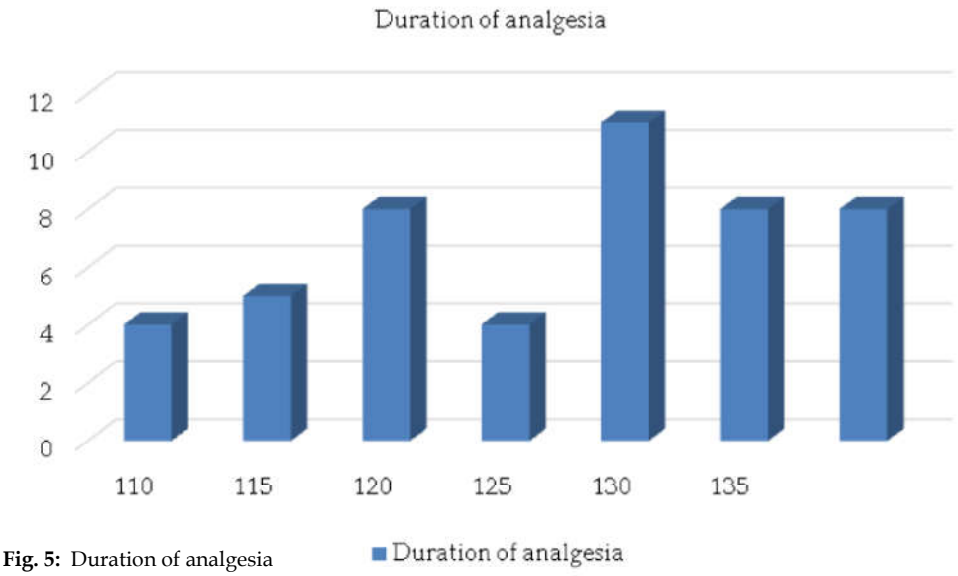


Fig. 5: Duration of analgesia

Table 9: Intra operative complications

Complications	No of cases	Percentage
Hypotension	10	20
Bradycardia	6	12
Shivering	5	10
Nausea & vomiting	8	16
Respiratory arrest	-	-
Cardiac arrest	-	-

Table 10: Postoperative complications

Complications	No of cases	Percentage
Backache	2	4
Nausea & vomiting	4	8
PDPH	-	-
Infections	-	-
Neurological sequelae	-	-

Discussion

Over a course of fifty years thoracic epidural anaesthesia has been utilizedin unintubated awake patients undergoing thoracic or upper abdominal surgeries for intraoperative anaesthesia & postoperative analgesia. Although thoracic epidural anaesthesia is technically difficult compared to lumbar spinal & epidural, thoracic epidural blockade provides good intraoperative & postoperative anaesthesia. Balzarena et al. found that regional anaesthesia had better outcome than general anaesthesia in thoracic & upper abdominal surgeries [8]. In areview of non-analgesic effects of thoracic epidural anaesthesia, studies have suggested that thoracic epidural anaesthesia attenuates the preoperative stress response after major surgery [9,10,11]. The possible mechanism of action include an improvement of left ventricular function by direct anti- ischemic effects, a reduction in cardiovascular complications, an advance on gastrointestinal function, and a reduction in pulmonary complication, as well as a positive impact on the coagulation system and the postoperative inflammatory response [10,11]. There was lesser incidence of pulmonary complications & deep vein thrombosis along with advantage of early ambulation & excellent postoperative analgesia [9]. Regional anesthesia will avoid airway instrumentation & problems associated with it such as bronchospasm, laryngospasm in cases with pulmonary diseases. This study was done on 50 patients posted for elective upper abdominal surgery. 0.5% bupivacaine was given in thoracic epidural space & effectiveness of thoracic epidural anaesthesia was checked in terms of onset, level & duration of sensory & motor blockade. Hemodynamic changes & intraoperative, postoperative complications were noted if any.

Onset of analgesia was noted as onset of sensory block. It was time taken from injection of drug in epidural space to attainment of upper level of block. In our study mean duration of onset of sensory blockwas found to be 17.4±2.1 min. In a study by Bromage it was found that onset of analgesia with 0.5% bupivacaine was 19 min [2]. Comparison of epidural ropivacaine & bupivacaine was done by Morrison et al. It was found that mean onset time for bupivacaine was 18±10 min [12]. Hence, the onset of analgesia in our study was comparable to other studies. Senagore et al used 8cc of 0.5% bupivacaine with 100 μg fentanyl for hemicolectomyin their study [13]. Sakura & collegeaues have used 10cc 2% lignocaine for upper abdominal surgeries in their study [14]. In our study we have used 10cc 0.5% bupivacaine. In this study we gave a constant volume of 10cc 0.55 bupivacaine to all patients at T_{8-9} interspace. Upper level of blockade was having a range of T_{1-6} with 62% of the patients having block at the level of T_{3-4}. Lower level of blockade was having having range of T_{12}-L_2 with 80% of patients having block at the level of T_{12}-L_1. The dosage of 0.5% bupivacaine was calculated in regard to the study done by Bromage [2]. In the study by Waters et al. it was found that local anaesthetic solution containing epinephrine enhanced duration of analgesia by 20% [15]. Bromage found that epidural block in thoracic region required 40% less local anaesthetic solution when compared to lumbar region [2]. Hence, this explains the lesser duration of analgesia as there is lesser drug used. Thoracic epidural anaesthesia causes blockade of cardiac sympathetic fibres arising from T_1-T_4, splanchnic fibres arising from T_6-L_1 causing decreased cathecholamine secretion & venous pooling [16]. All these cause decreased cardiac output, decreased systemic vascular resistance & hence hypotension occurs [17,18]. With the use of bupivacaine there was an observation that there is lesser tendancy for rapid fall in blood pressure as bupivacaine has slower onset. Pre-operatively average MAP was found to be 91.6±9.1 mmHg & it decreased to minimum of 83.8±13.5 mmHg at 30 min. Later on compensatory mechanism begin to act & bring back average MAP to pre-operative levels. Similar changes were seen in systolic BP & diastolic BP. 10 cases (20%) had significant hypotension (>20% of basal reading) & were treated with Inj Mephertermine 6 mg i.v bolus. Mac Lean & Colleagues found that the fall in MAP was 15-20% in patients receiving high thoracic block [19]. Studies have shown that

thoracic block upto level of T_1 cause blockade of cardiac sympathetic fibres [16]. 6 patients in the study had bradycardia (heart rate < 50 bpm). They were treated with inj atropine 0.6 mg i.v, elevation of foot end & inj mephentermine 6 mg i.v. Blockade of cardiac sympathetic fibres, decreased venous return due to hypotension & increase in vagal tone due bowel traction are causes for bradycardia in this study. Hypotension (20%) & bradycardia (12%) were the intraoperative complications for which Inj mephentermine & inj atropine was given i.v. 10% of patients developed shivering due to vasodilatation & were treated with inj tramadol 1 mg/kg iv. 16% of the patients developed nausea & vomiting due to traction to stomach & lower esophagus following vagus nerve stimulation. It was treated with inj ranitidine 50 mg iv & inj metoclopramide 10 mg iv. Incidence of technical complications like dural puncture, bleeding & difficulty in threading catheter was comparable to study done by Giebler RM [20]. In our study we had 2 cases of dural puncture but no incidence of epidural hematoma, bleeding, infection & neurological sequelae. Giebler RM in his study on 4185 patients regarding neurological sequelae in thoracic epidural catheterization showed an incidence of 3.6% of neurological sequelae whereas DeLeon-Casasola et al. showed incidence of 0.07% [21]. These results are comparable to our study.

Conclusion

Thoracic epidural anaesthesia is an excellent option for upper abdominal surgeries. It provides good intraoperative anaesthesia & postoperative analgesia facilitating early mobilization & recovery postoperatively. It prevents the risks associated with general anesthesia such as deep vein thrombosis & pulmonary complications. Hemodynamic changes were significant but can be managed satisfactorily. Hence we conclude that thoracic epidural anaesthesia should be a part of the armamentarium of anaesthesiologists in upper abdominal surgeries.

References

1. Buggy DJ, Smith G, Epidural anaesthesia and analgesia: Better outcome after major surgery? BMJ 1999;319:530-31.
2. Bromage RP. Epidural Analgesia, Philadelphia: W.B. Saunders company; 1978.
3. Dawkins CJM, Steel G C. Thoracic epidural block for upper abdominal surgery. Anaesthesia. 1971;26:41-9.
4. Crawford OB. Peridural anesthesia for thoracic surgery. NY state J Med. 1952;52:26-37.
5. Stanton H. High thoracic epidural with sufentanyl for post-thoracotomy pain. Reg Anesth. 1988;13:62-6.
6. Zwarts SJ. The effect of continuous epidural analgesia with sufentanyl and bupivacaine during and after thoracic surgery on the plasma cortisol concentration and pain relief. Reg Anesth. 1989;14:183-7.
7. Waurick R. Van Aken H. Update in thoracic epidural anaesthesia. Best Pract Res clin Anaesthesiol. 2005;19(2):201-13.
8. Belzarena SD. Comparative study between thoracic epidural block & general anaesthesia for oncologic mastectomy. Revista brasileira de anestesiologia. 2008 Dec;58(6):561-8.
9. Kozian, Schilling AIF, Hachenberg T, Thomas. Non-analgesic effects of thoracic epidural anaesthesia. Current opinion in Anaesthesiology. 2005;18(1):29-34.
10. Gould TH, Grace K, Thorne G, Thomas M. Effect of thoracic epidural anaesthesia on colonic blood flow. Br J Anaesth. 2002;89(3):446-51.
11. Kapral S, Gollmann G, Bachmann D. Prohaska B, Likar R. Jandrasits O et al. The effects of thoracic epidural anesthesia on intraoperative visceral perfusion andmetabolism. Anesth Analg. 1999 Feb; 88(2):402-6.
12. Morrison LMM, Emanuelsson BM, McClure JH. Efficacy & kinetics of extradural ropivacaine: comparison with bupivacaine. Br J Anaesth. 1994;72:164-7.
13. Senagore AJ, Whalley D, Delaney CP, Mekhail N, Duepree HJ, Fazio VW. Epidural anaesthesia-analgesia shortens length of stay after laparoscopic segmental colectomy for benign pathology. Surgery 2001;129(6):672-6.
14. Sakura S, Saito Y, Kosaka Y. Effect of extradural anaesthesia on ventilatory response to hypoxaemia. Anaethesia. 1993;48:205-9.
15. Waters HR, Rosen N, Perkins DH. Extradural blockade with bupivacaine. A double blind trial of bupivacaine with adrenaline 1/200000 & bupivacaine plain. Anaesthesia. 1970;25;184-9.
16. Wang CM, Ko WR, Chao CC, Lin CH, Chen MH, Lin HJ et al. Thoracic epiduralanesthesia for major abdominal surgery: a retrospective study. Acta Anaesthesiol Sin. 1994;32(1):31-6.
17. Goertz A, Heinrich H, Seeling W. Baroreflex control of heart rate during high thoracic epidural anesthesia. Anaesthesia. 1992;47:984-87.
18. Claeys MA, Verborgh C, Delvaux G. Thoracic epidural bupivacaine- Fentanyl anesthesia for percutaneous cholecystolithotomy in high risk patients. Reg Anaesth. 1992;17(2):87-90.
19. Mc Lean APH, Molligan GW, Otton P, Mc Lean LD.

Hemodynamic alterationsassociated with epidural anaesthesia. Surgery. 1967;20:117-9.

20. Giebler RM, Scherer RU, Peters J. Incidence of Neurologic complications related to Thoracic epidural catheterization. Anesthesiology. 1997;86:55-63.

21. De Leon- Casasola OA, Parker B, Lema MJ, Harisson P, Massey J. Postoperative epidural bupivacaine-morphine therapy experience with 4,227 surgical cancer patients. Anaesthesiology. 1994;81:368-75.

Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(1) (Part - II): 341-347
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.47

A Retrospective Study of Serial Inspection of ACLS Ambulances in a Tertiary Care Facility

Wasnik Seema B[1], Kaur Mohandeep[2], Dhir Vinod Bala[3], Mittal Rajishth[4], Singh Tarundeep[5], Sikri Himanshu[6], Nisha[7]

[1]Senior Anaesthesiologist [2,3]Professor [4]PG 2nd Year Student [5]Junior Resident [6]Medical officer [7]Senior Resident, Dept. of Anesthesia, Dr. Ram Manohar Lohia Hospital, New Delhi, Delhi 110001, India.

Abstract

Aim: To maximize availability of Ambulance equipment before dispatch. *Design:* Retrospective observational study. *Material and Methods:* A team of doctors, nurses and paramedics of our tertiary care central government hospital of capital city in a lower middle income economy background country were assigned the task of inspection of ambulances prior to sending these for a national event. These ambulances were inspected for preparedness for patient care. The tertiary care center was the nodal center for inspection where ambulances from different organizations like CATS and corporate tertiary care hospitals were assembled for inspection on day 1, day 3 and day 7, while on the 8th day these ambulances were dispatched for patient care. Ambulances were checked consequetively for three days according to existing standardized check list [3]. A separate logistic cell was managed by the inspection team for procurement and maintenance of equipment. The ambulance pilot supervisor was responsible for checking the mechanical component of ambulances. *Statistical Analysis*: Quantitative variables were compared using Wilcoxon signed- rank test (as the data sets were not normally distributed) across follow up. A p value of <0.05 was considered statistically significant. *Results*: In between series of inspections, the task of functional completion of ambulance equipment significantly improves thereby pointing out to the success of methods employed in the present study. Our inspection was successful in terms of maximizing the availability of life saving equipment. *Conclusions and Recommendation*: A series of Ambulance inspection is essential for ascertaining the availability of disposable and consumable items in a fully equipped ACLS ambulance. The Ambulance team should be open to adding new evidence-based life- saving equipment to the existing standardized checklist.

Keywords: Advanced Cardiac Life Support Ambulances; Inspection; Shortfalls; Stock; Emergency Medical Services; Pre-hospital Care.

How to cite this article:

Wasnik Seema B, Kaur Mohandeep, Dhir Vinod Bala et al. A Retrospective Study of Serial Inspection of ACLS Ambulances in a Tertiary Care Facility. Indian J Anesth Analg. 2019;6(1):341-347.

Introduction

The researchers felt the importance of this study as very little data was available in literature about the standard of equipment inside the Ambulances**.** The importance of first golden hour**,** and platinum minutes [1] in managing patients of Road Traffic Accident (RTA), acute coronary syndrome and stroke necessitates the importance of state of art facility inside the Ambulances. The ACLS ambulance plays pivotal role in quick management of victims in the pre-hospital scenario and rapid transfer to appropriate and nearest health care facility.

Corresponding Author: Mohandeep Kaur, Professor, Dept of Anesthesia, Dr. Ram Manohar Lohia Hospital, New Delhi, Delhi 110001, India.
E-mail: mdkaur@gmail.com
Received on 26.10.2018, **Accepted on** 14.11.2018

The shortage of life saving disposable and equipment stock in ambulances can affect the performance of medical and paramedical staff adversely by several folds as pre-hospital emergency management needs quick and protocol-based management and rapid transport of victim to nearest health care facility [2].

Materials and Methods

Twenty-three ACLS ambulances were inspected for life saving equipment on Day 1, Day 3 and Day 7 by a team of doctors and paramedics. These ambulances were dispatched for patient care on Day 8.

The inspection was carried out by checking the ambulance equipment of 23 ACLS ambulances as per the existing standardized checklist [3]. After each inspection, the team tried to fill in the deficiencies. Moreover, a separate logistic cell was setup by tertiary care facility to manage procurement of various items, liaison for repair of equipment, arrangement for refilling of oxygen cylinders and specific items.

All the 23 ambulances were from different organizations and therefore there was variation in stock of equipment. To overcome this variation and shortage of items, the logistic team prepared emergency kits of life saving medicines, consumables and disposables for each of the 23 ambulances. This emergency lifesaving kit was handed over to ambulance staff before the dispatch of ambulances on the 8th day.

A team of doctors, paramedics and Ambulance Supervisor and Ambulance pilots performed inspection of various equipment of 23 Ambulances on Day 1, Day 3 and Day 7 before the dispatch of Ambulances on Day 8. Some of the team members were assigned the task of managing the logistic cell.

Item 1-23 were fixed items inside the Ambulance. These included defibrillators, cardiac monitor with ECG electrodes, sphygmomanometer, glucometer, stethoscope, Ventilator, AED with Pads suction machine, spine board, cervical collar, scoop stretcher, immobilization devices, torch, electronic thermometer, bag valve mask resuscitator, Macintosh laryngoscope with blades, oxygen cylinder type D with regulator with key, Oxygen cylinder type A with key, oxygen flow meter, IV stand, pneumatic splints with pump, nebulizer and safety items like fire extinguishers.

Certain items like auto pulse, cricothyrotomy set with jet ventilator, central venous catheters and intraosseous needles are desirable and lifesaving but were not mentioned in the existing standard checklist.

Availability of Trained staff (item 33), mechanical fitness of Ambulance (item 40) and maintenance of records is a standard pre-requisite.

Items 22-32 and 34-39 were disposable and consumable items like airway adjuncts, medicines like lifesaving injections, first- aid material including tablets, sprays, ointments, dressing material, antiseptics, disinfectants, waste disposal color-coded containers and Personal Protective Equipment (PPE).

Moreover, inspection of equipment was followed by organizing procurement of equipment for ambulances and filling up the existing deficiencies. The inspection team had double responsibility of finding shortcomings in equipment, mechanical component of ambulances and making arrangement for the same before dispatch. The inspection team also prioritized inspecting safety aspect of patient care in the pre-hospital scenario.

Thus, this study helped us to understand the deficiencies in ACLS Ambulances and fulfill the demands that arose after identifying the shortages according to the standardized checklist.

The result of the study was analyzed statistically.

Statistical Analysis

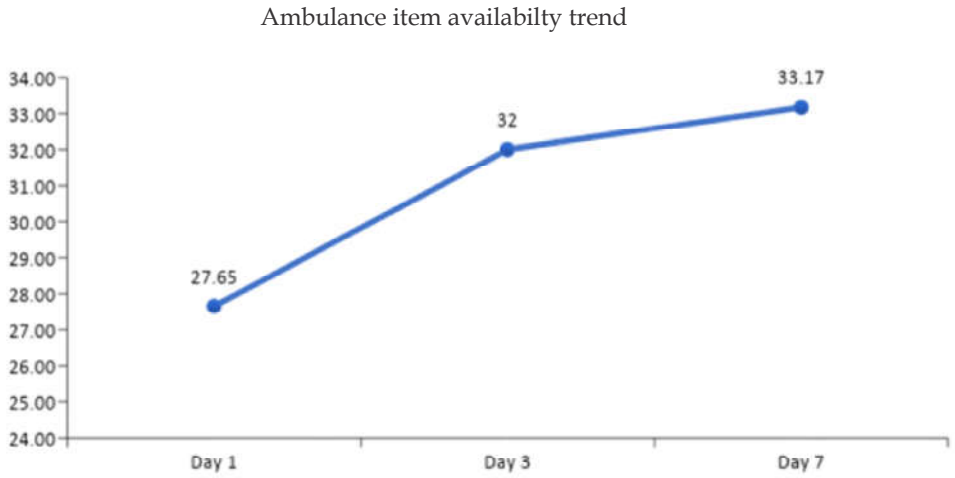
Continuous variables were presented as mean±SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non-parametric test was used. Quantitative variables were compared using Wilcoxon signed- rank test (as the data sets were not normally distributed) across follow up. A p value of <0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

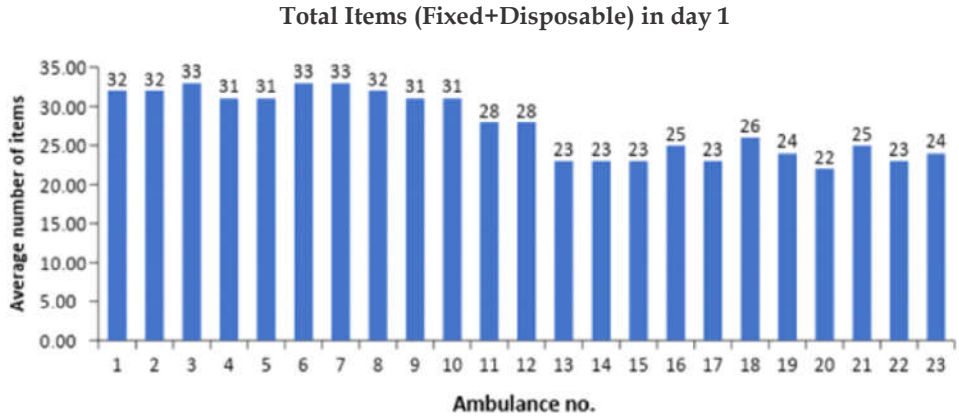
Availability of total items increased from 1st day of inspection to 7th day of inspection as shown in graph1 and table 1 which was statistically significant. ($p < 0.0001$). Individual total (fixed and disposable) items in each of the 23 ambulances on 3 days of inspection shown in Graphs 2, 3 and 4 respectively.

Availability of fixed and disposable items increased on subsequent days which was statistically significant as shown in Table 2 ($p < 0.083$) and Table 3 ($p < 0.0001$) respectively.

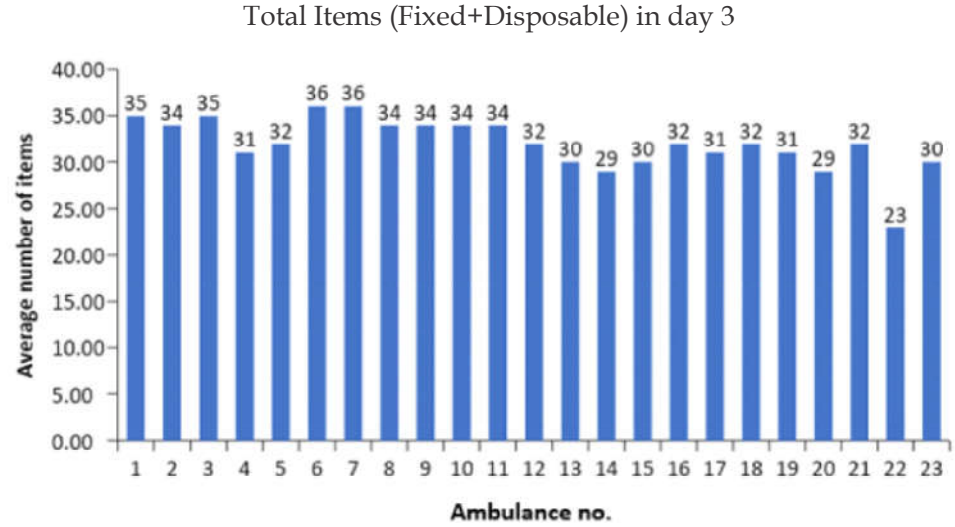
Fixed items in each 23 ambulances on 3 days of inspection are shown in Graphs 5, 6 and 7. Disposable items in each 23 ambulances on 3 days of inspection are shown in Graphs 8,9 and 10.



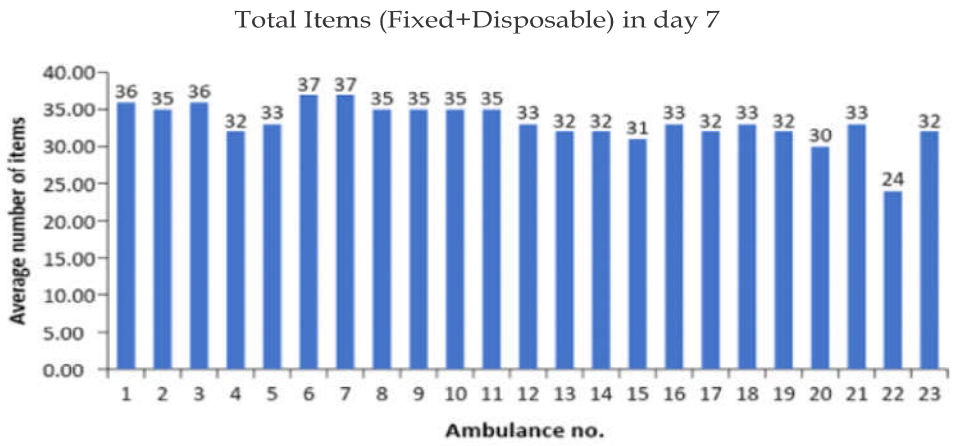
Graph 1: Showing total ambulance item availability trend



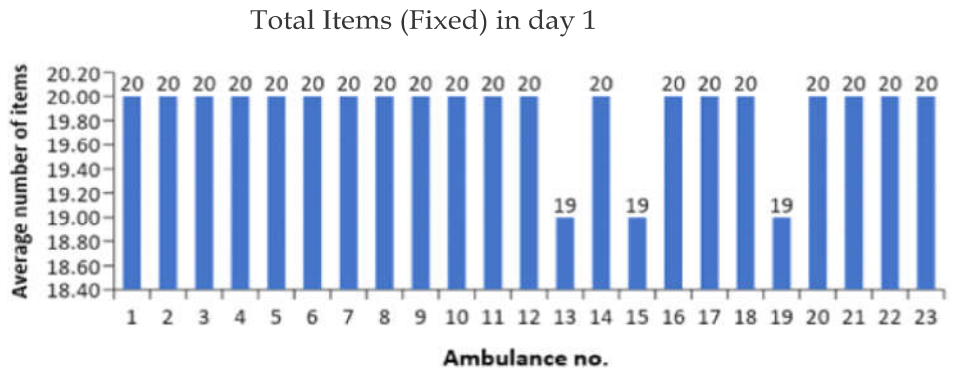
Graph 2: Total items on day 1



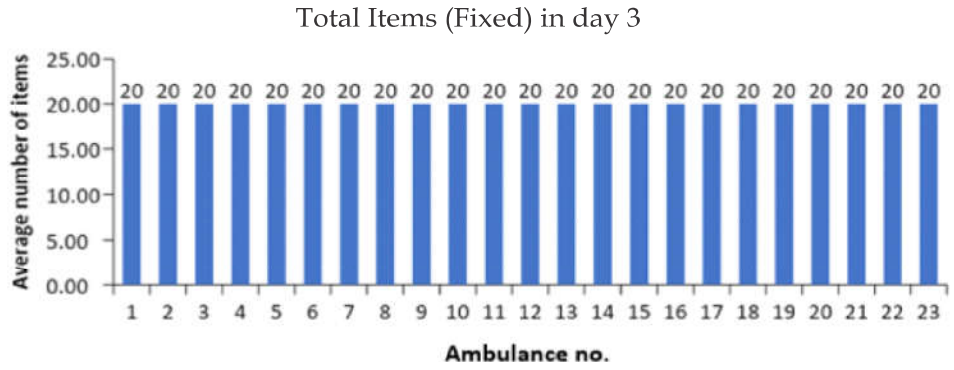
Graph 3: Total items on day 3



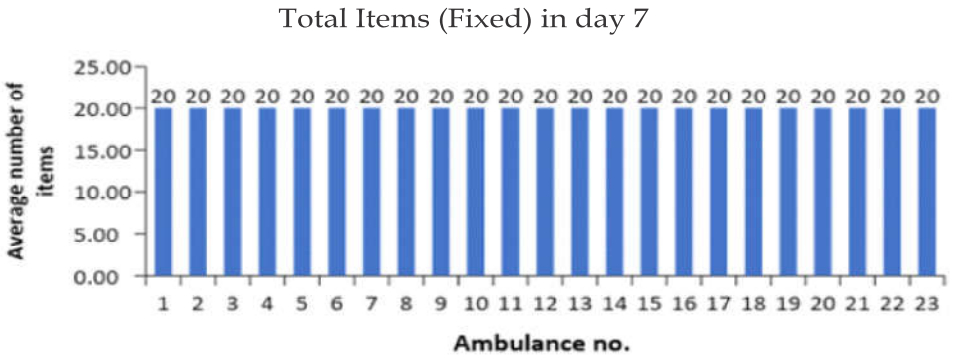
Graph 4: Total items on day 7



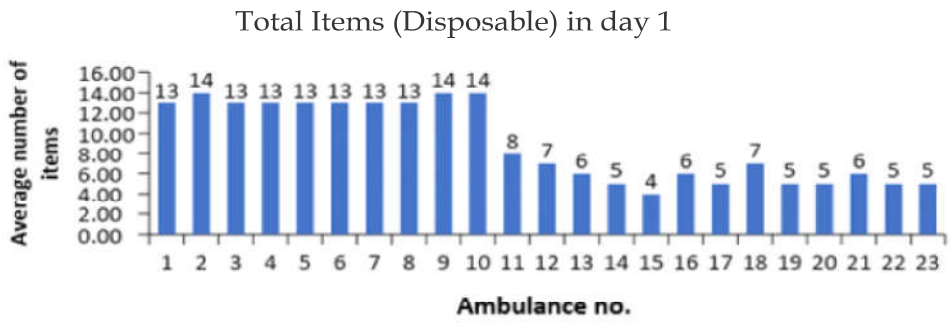
Graph 5: Total fixed items on day 1



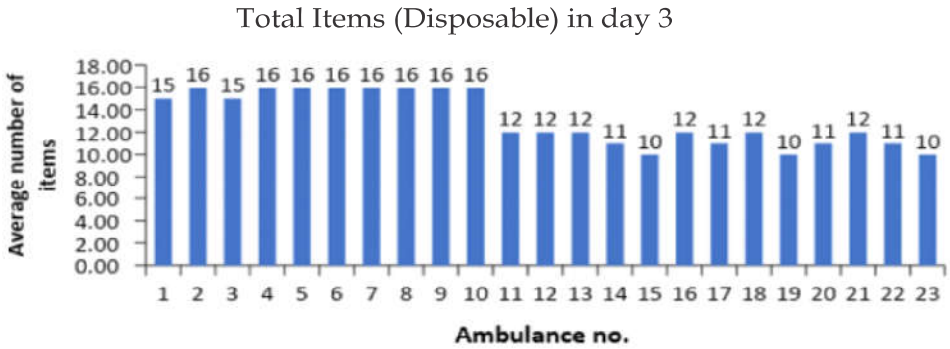
Graph 6: Total fixed items on day 3



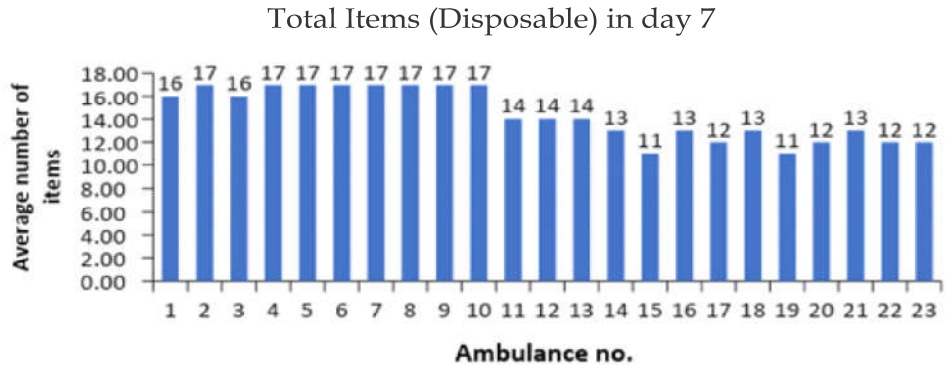
Graph 7: Total fixed items on day 7



Graph 8: Total disposable items on day 1



Graph 9: Total disposable items on day 3



Graph 10: Total disposable items on day 7

Table 1: total equipments

	Sample size	Mean ± Stdev	Median	Min-Max	Inter quartile Range	P value
Day 1	23	19.87 ± 0.34	20	19-20	20 - 20	
Day 3	23	20 ± 0	20	20-20	20 - 20	0.083
Day 7	23	20 ± 0	20	20-20	20 - 20	0.083

Table 2: Fixed equipments

	Sample size	Mean ± Stdev	Median	Min-Max	Inter quartile Range	P value
Day 1	23	27.65 ± 4.11	28	22-33	23.250 - 31.750	
Day 3	23	32 ± 2.89	32	23-36	30.250 - 34	0.0001
Day 7	23	33.17 ± 2.77	33	24-37	32 - 35	<.0001

Table 3: Disposable equipment

	Sample size	Mean ± Stdev	Median	Min-Max	Inter quartile Range	P value
Day 1	23	9 ± 3.95	7	4-14	5 - 13	
Day 3	23	13.22 ± 2.41	12	10-16	11 - 16	<.0001
Day 7	23	14.44 ± 2.27	14	11-17	12.250 - 17	<.0001

Discussion

Fixed items were 99 percent stocked in comparison to consumable and disposable items on Day 1 of the inspection.

Defibrillator is a life saving device. Its functional working, battery backup, ECG electrodes **(**disposable item) was checked during inspection AED and pads (disposable item**)** were checked.

In our study it was found that ECG electrodes were not available in one ambulance and AED pads in another ambulance out of 23 ambulances. This result appears to be statistically insignificant, however, clinically it is very significant. Although, this finding is not statistically significant, without ECG electrodes, one cannot analyze the rhythm of heart. 12 lead ECG performed in pre-hospital care reduces door to balloon time improving prognosis in patients with short ischemic time in STEMI [4].

According to the American Heart Association (AHA), use of an AED is the third and crucial step in the cardiac arrest chain of survival [5].

Again, in this study we found that AED pads were not stocked in one out of twenty - three ambulances. This may be statistically insignificant but clinically the equipment becomes worthless in life saving situations.

Thus, fixed items must be checked individually for attached disposable items for the entire equipment to be functional and lifesaving.

Disposable items associated with fixed items need careful replenishment according to this study.

In our study, none of the ambulances was equipped with Auto Pulse (Automated CPR machine). Manual CPR can be of poor quality because of rescuer fatigue, multitasking in ambulance, and transportation of victim on stretcher, interruptions in movement of patient and variations in technique of CPR.

Successful Cardiopulmonary resuscitation depends on right compressions, recoil, right technique of CPR and minimal interruptions.

One of the best predictors of ROSC is attaining CPP of greater than 15 mm of Hg. Interruptions during CPR drastically drops CPP. Multitasking by medical and paramedical personnel inside the moving ambulance can cause interruptions in CPR. Moreover, if the victim is managed on a stretcher then the possibility of interruptions is considerable [6].

Mechanical CPR like Auto pulse can deliver high quality CPR when the EMS personnel is multitasking or restrained [7].

In this study we found that none of the ambulances had any new item added to the existing checklist. Ideally with the advances in equipment development, the ambulance team should always be open to addition of latest evidence-based lifesaving equipment like auto pulse.

Another problem of adding new equipment to the existing list is difficulty in procurement in low middle income economy group countries.

Moreover, in this study we found that none of the Ambulances had NIV face mask in the equipment. Non-invasive mechanical ventilation can be used in emergency services in acute respiratory failure cases caused by acute pulmonary edema and chronic obstructive pulmonary disease exacerbation, but patients with variables related to a higher percentage of endotracheal intubation should be specially monitored [8]. Our study showed that the safety equipment like sirens and fire extinguishers and equipment like ventilator and defibrillator, monitors were better maintained in comparison to disposables, consumables including PPE and airway adjuncts.

On first and second inspection, airway adjuncts, ointments, medicines and dressing material were deficient in ambulances no. 12-23 in our study. The ambulance team faces many challenges in providing patient care while maintaining their own safety along with their patient safety [9]. All contagious diseases require Personal Protective Equipment (PPE) [10]. The inspection team in this study found that disposable, consumables, medicines and tablets fell short as per the standard checklist. Unpredictable scenarios can emerge while working in ambulances like fire in ambulances, ambulance crashes and power failure. Disposable and consumable items need constant replacement after consumption. A regular indent from stores of institutions of such items is essential for standard optimum care of casualty. These items were satisfactory on the third inspection done on 7th day.

In this study the inspection team studied the cleanliness of ambulance and its equipment.

After removal of debris from the ambulance decontamination was done. In this study the Ambulance cleaning plan included a cleaning schedule. Providers wiped down equipment that was in contact with a patient before the next call, focusing on what was used for patient care or was in contact with the patient during patient care. Ambulance is meant to be cleaned at the end of the day. Completely empty the vehicle at the end of the week for cleaning it thoroughly [11].

It was found that ambulance cleanliness and biomedical waste management was of optimum standards in ambulance number 1-10 and rest were clean on the third inspection i.e. on the 7th day of inspection (Ambulance no 11 to 23).

In this study it was found that ambulance number 1-10 had special demand of intraosseous needle. The physician in charge of ambulances placed a special demand for this item. Likewise, Special demands can be placed for items like cricothyroidotomy sets and open tracheostomy sets, central venous catheters depending on the skill and training of individual physician.

Mechanical Component of the Ambulance

The mechanical supervisor found that all ambulances were fit, safety devices were working and in place as advised in the checklist except for one ambulance which had non- availability of fire extinguisher during first and second inspection. One ambulance had arranged fire extinguisher at the last moment. (Ambulance No 23).

Conclusion

A series of ambulance inspection is essential for availability of disposable and consumable items. The fixed items in the ambulance need regular service and disposable items attached to fixed items in the ambulances require stock wise replacement. The ambulance team should be open to adding new evidence-based life- saving equipment to the existing standardized checklist. Setting up of separate logistic cell, exclusively for procurement of ambulance equipment and maintenance for the same, is an additional requirement.

Acknowlegement

Ambulance pilot supervisor Mr. TS Bisht and emergency sister in charge Mrs. Geeta for supervising and arranging various items for surgery. Senior Resident Dr Nisha, Post graduate's Dr Jess and Dr Sachin for inspecting the ambulances.

References

1. Rotaru L, Colata F. The Management in ' The Golden hour" and the survival of the Poly traumatized patient. Journal of Experimental Medical & Surgical Research. 2010;17:36-43.
2. Soodabe V, Ehsan K, Majid P. A comparative study of road ambulances equipment based on the national standards in Guilan province. International Journal of Health system and Disaster Management 2013;11: 2-6.
3. American college of Surgeons: Equipment for Ambulances. Available from: https://www.facs.org/~/media/files/.../ambulance.ashx;2009.
4. Adam W, Yuvaraj M, Ian J, Bill B, Edward W, George B et al. Prehospital 12-lead ECG to triage ST-elevation myocardial infarction and emergency department activation of the infarct team significantly improves door-to-balloon times: ambulance Victoria and Monash HEART Acute Myocardial Infarction (MonAMI) 12-lead ECG project. Circ Cardiovasc Interv. 2009;2(6):528-34.
5. Ross A, Siobhan P, Thomas R, Tom A, David B, Jason M et al. Impact of Bystander Automated External Defibrillator Use on Survival and Functional Outcomes in Shockable Observed Public Cardiac Arrests Circulation. 2018;137:2014-113.
6. Cyprus C. The merits of mechanical CPR: Do mechanical devices improve compression consistency and resuscitation outcomes? JEMS. 2012;37(9):24-9.
7. Franois X, Papa J, Sonja C, Florence T, Claire B, Patrick P et al. Effect of the Auto Pulse (TM) automated band chest compression device on hemodynamics in out-of-hospital cardiac arrest resuscitation. Intensive Care Medicine. 2010; 36(7):1256-60.
8. Juliana N, Lair Z, André M, Carolina K, Ivete A. Use of non-invasive ventilation in acute pulmonary edema and chronic obstructive pulmonary disease exacerbation in emergency medicine: predictors of failure. Rev. bras. ter. Intensive. 2012;24:3.
9. Carlotta M, Larry W, Thomas B. A Research Study of Ambulance Operations and Best Practice Considerations for Emergency Medical Services Personnel. Department of Homeland Security (DHS) Science and Technology Directorate First Responders Group 2015.
10. Shailaja D, Sunil KS, Anita K. Ebola virus: Awareness about the disease and personal protective measures among junior doctors of a tertiary hospital in Delhi, India; Int JMed Public Health. 2015;53:217-24.
11. Teresa M. How Clean is Your Ambulance? The truth behind cleaning chemicals; JEMS 2012.
12. Carlotta M, Larry Thomas B. A Research Study of Ambulance Operations and Best Practice Considerations for Emergency Medical Services Personnel. First Responders group, Department of Homeland Security (DHS) Science and Technology Directorate 2015.

Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(1) (Part - II): 349-352
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.48

Comparison of Intravenous Clonidine with Intravenous Lignocaine for Attenuation of Endotracheal Intubation Induced Haemodynamic Response

Rajni Kumari[1], Ajay Kumar[2], Shipra Aggarwal[3]

[1-3]Assistant Professor, Department of Anaesthesiology, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi, Delhi 110029, India.

Abstract

Background: Endotracheal intubation is the standard practice for general anaesthesia inspite of many supraglottic airway devices have arrived. Various drugs have been used till date to attenuate the hemodynamic response to endotracheal intubation. This study compared the effects of intravenous Clonidine (2.5 µg/kg) and Lignocaine (1.5 mg/kg), for attenuation of hemodynamic response in laryngoscopy and endotracheal intubation. *Methods*: Ninety patients of ASA class I & II were divided into two groups of 45 each. Group L patients received injection Lignocaine and Group C patients received injection Clonidine. Hemodynamic parameters were monitored by using multiparameter monitor before intubation and at 1, 3, 5 and 10 minutes after endotracheal intubation. *Results:* No significant difference between two groups was observed in terms of hemodynamic parameter including heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure. Pretreatment with injection Clonidine is equally better alternative to lignocaine with similar advantages for blunting the undesirable hemodynamic response associated with laryngoscopy and intubation.

Keywords: Clonidine; Lignocaine; Hemodynamic response; Intubation.

How to cite this article:

Rajni Kumari, Ajay Kumar, Shipra Aggarwal. Comparison of Intravenous Clonidine with Intravenous Lignocaine for Attenuation of Endotracheal Intubation Induced Haemodynamic Response. Indian J Anesth Analg. 2019;6(1):349-352.

Introduction

Laryngoscopy and tracheal intubation predictably leads to hypertension and tachycardia first described by Reid and Brace in 1940 [1]. The rise in pulse rate and blood pressure is usually transient, variable and unpredictable. Usually these changes are well tolerated by healthy individuals but may increase morbidity and mortality in patients with hypertension, coronary artery disease or intracranial hypertension. Various measures like local anaesthetic spray, nerve blocks, I.V. drugs like lignocaine, magnesium sulphate and recently α_2 agonist clonidine have been tried to prevent this undesired response of endotracheal intubation.

The hemodynamic response can be attenuated by intravenous administration of narcotics like fentanyl [2]. Intravenous lignocaine may be used to 'blunt' the laryngoscopy response, although some studies have called the effectiveness of lignocaine in this setting into doubt [3]. Hypotensive agents, including sodium nitroprusside, nitroglycerine, hydralazine, β-blocker, and calcium channel blocker have also shown to effectively attenuate

Corresponding Author: Rajni Kumari, Assistant Professor, Department of Anaesthesiology, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi, Delhi 110029, India.
E-mail: shobhanachu@gmail.com
Received on 24.10.2018, **Accepted on** 14.11.2018

the transient sympathetic stimulation. Clonidine an α_2 agonist, has been successfully used to blunt laryngoscopy response, but the adequate dose and time of administration is still not validated. If a small dose of clonidine, administered shortly before intubation, can prevent this hemodynamic response, it is worth trying. In this study we will compare the effects of intravenous clonidine (2.5 µg/kg) and intravenous lignocaine (1.5 mg/kg), for attenuation of hemodynamic response in laryngoscopy and endotracheal intubation.

Methods

Randomized double blinded clinical trial was performed on ninety patients of either of ASA grade I & II within age group of 18 to 60 years, undergoing elective abdominal surgery under general anaesthesia. For this study written informed consent was taken from hospital's ethical committee and patients as well. Patients having any abnormality in airway, history of allergy to study drug and taking drugs affecting autonomic nervous system were excluded from the study. Preoperative heart rate, blood pressure, respiratory rate were noted down. The patients were randomly distributed into two groups each having 45 patients. Group L patients received intravenous Lignocaine (1.5 mg/kg) andgroup C patients received intravenous Clonidine (2.5 ug/kg). Randomization was by means of computer generated codes. All members of the surgical team, the patients, and the anaesthetist were unaware of group allocation.

The patients were taken in preoperative room 1 hour prior to surgery and intravenous infusion was started with a cannula of 18G. NIBP, ECG and pulse oxymeter probe were connected and baseline readings of all the vitals were recorded. Patients were preoxygenated with 100% oxygen for 3 minutes. Study drug was injected intravenously slowly after then patient was induced with intravenous thiopentonein incremental doses until loss of eyelash reflexes followed by injection vecuronium 0.12 mg/kg. Ventilation was done with 100% oxygen up to 90 seconds and then patients were intubated with endotracheal tube and bilateral air entry was confirmed tube was fixed and secured. At fifteen minutes, fentanyl (2.5 µg/kg) was given and after 20 minutes surgery was allowed to commence. Anaesthesia was maintained with N_2O:O_2 (2:1) with 0.5% isoflurane with IPPV.

Hemodynamic parameters like HR, SBP, DBP, and MAP were recorded by using multiparameter monitor before intubation and 1, 3, 5, and 10 minutes afterwards. After completion of surgery neuromuscular block was reversed by neostigmine and glycopyrrolate combination in titrated doses intravenously. After adequate recovery patient was extubated following suction. Bradycardia (HR<60) and hypotension (SBP <90) were also recorded. All the statistical analysis was performed using the SPSS package (version 19, SPSS, Chicago, II). The statistically significant level was P< 0.05.

Results

Ninety patients were randomly distributed in two groups Clonidine and Lignocaine of either sex between 18 to 60 years with ASA I & II grade.

Table 1: Demographic data distribution in different groups

	Clonidine Group	Lignocaine Group	P value
Age (Years) (Mean ± SD)	42.88±8.92	36.4±11.06	> 0.05
Weight (Kgs) (Mean ± SD)	54.13±7.08	50.9±6.89	> 0.05
Gender (M/F)	25/15	19/21	> 0.05

Data expressed as Mean ± SD

As evident from the Table 1, both the groups were statistically comparable in terms of age, weight and sex distribution. (p value >0.05).

There was no statistically significant difference between the two groups of patients regarding HR, SBP, DBP and MAP before intubation and 1,3,5 and 10 minutes after tracheal intubation(Tables 2-5).

Table 2: Comparison of Mean Heart Rate between the study groups (n = 45)

Heart Rate/min	Clonidine Group	Lignocaine Group	P value
Before Intubation	92.3±15.02	89.7±12.1	>0.05
I minute after intubation	95.4±13.0	102.5±16.3	>0.05
3 minutes after intubation	87.5±14.3	99.3±14.7	>0.05
5 minutes after intubation	82.8±12.0	93.7±13.5	>0.05
10 minutes after intubation	80.2±15.6	89.8±15.5	>0.05

Data expressed as Mean ± SD.

Table 3: Comparison of Systolic Blood Pressure between the study groups (n = 45)

Systolic Blood Pressure(mmHg)	Clonidine Group	Lignocaine Group	P value
Before Intubation	117.4 ± 8.9	118.7± 5.2	>0.05
I minute after intubation	120.7± 5.4	138.8±17.6	>0.05
3 minutes after intubation	115.8 ±7.3	125.3±11.7	>0.05
5 minutes after intubation	110.8±6.6	120.7±7.5	>0.05
10 minutes after intubation	105.7±7.9	119.7±6.6	>0.05

Data expressed as Mean ± SD

Table 4: Comparison of Diastolic Blood Pressure between the study groups (n = 45)

Diastolic Blood Pressure(mmHg)	Clonidine Group	Lignocaine Group	P value
Before Intubation	74.9±4.5	76.8±4.1	>0.05
I minute after intubation	78.8±5.6	86.6±7.7	>0.05
3 minutes after intubation	73.9±4.9	84.5±6.5	>0.05
5 minutes after intubation	72.6±4.4	81.3±5.7	>0.05
10 minutes after intubation	72.9±4.8	77.7±3.3	>0.05

Data expressed as Mean ± SD

Table 5: Comparison of Mean Blood Pressure between the study groups (n = 45)

Mean Blood Pressure(mmHg)	Clonidine Group	Lignocaine Group	P value
Before Intubation	88.3±6.0	90.6±4.4	>0.05
I minute after intubation	92.0±5.5	100.8±11.2	>0.05
3 minutes after intubation	87.6±5.7	97.6±8.2	>0.05
5 minutes after intubation	84.5±5.1	94.5±6.3	>0.05
10 minutes after intubation	83.1±5.8	91.2±4.4	>0.05

Data expressed as Mean ± SD

Discussion

Intubation is associated with a cardiovascular response of elevated blood pressure and pulse, occasional dysrhythmia, coughs reflex, increase intracranial pressure, and increased intraocular pressure. Various efforts have been made to attenuate this adverse phenomenon. The present study showed that both intravenous clonidine and lidocaine were equally effective in reducing the hemodynamic stress responses (HR, SBP, DBP, and MAP) to laryngoscopy and tracheal intubation.

Endotracheal intubation is a stressful noxious stimulus, resulting in a marked increase in the sympathetic amines (adrenaline and noradrenaline) leading to complications, especially in patients with cardiovascular diseases. These complications include increases in blood pressure and heart rate that may cause tachyarrhythmia. In normal patients, these hemodynamic responses are generally well-tolerated, whereas in patients with cardiovascular diseases, they may cause cerebral haemorrhage, left ventricular failure, and in rare conditions, myocardial ischemia [4,5,6].

Our study confirm and extend the results of other investigators who showed that clonidine and lidocaine separately were effective in blunting reflex tachycardia and hypertensive responses associated with intubation and laryngoscopy in patients undergoing general anaesthesia [7,8,9-16].

Idit Matot et al. [17] used oral clonidine 300 µg and noted significant decrease in HR, SBP, DBP, and MAP after laryngoscopy and intubation. In our study we found increase in HR, SBP, DBP, & MAP in a dose of 2.5 ug/kg this may be due to difference in dose and route of administration.

Davies DS et al. [18] showed that clonidine has been tried in various oral doses and infusion forms. As bioavailability after oral intake varies between 70% and 90%, we choose the IV route of administration to relate pharmacodynamic effects. So our study was designed to find out its efficacy for attenuation of haemodynamic response through IV bolus dose. Furthermore as an intravenous route is available therefore this route is preferable for its 100% bioavailability.

A study conducted by Routray et al. [19] which compared fentanyl-lidocaine with fentanyl-clonidine on hemodynamic responses to tracheal intubation in 40 hypertensive patients. No significant differences were found between the hemodynamic parameters of two groups and concluded that both the fentanyl clonidine and fentanyl lidocaine combinations effectively decreased the stress response to endotracheal intubation. Our study correlated positively with this study.

A study conducted by Kumari et al. [20] compared clonidine and midazolam as premedication agents. Administration of clonidine before induction and intraoperatively improves perioperative hemodynamic stability. Lignocaine has been found to attenuate the hemodynamic response to endotracheal intubation. Clonidine premedication is considered to be safe without episodes of hypotension, bradycardia, and nausea and vomiting. In present study, both clonidine and lignocaine lower the hemodynamic response to intubation but clonidine was found to be more effective in attenuating the sympathetic response.

Conclusions

Pretreatment with both clonidine 2.5 ug/kg and lignocaine 1.5 mg/kg five minutes before intubation can be used effectively in clinical practice to attenuate the hemodynamic response to laryngoscopy and endotracheal intubation. Though lignocaine has widespread application, the study proves that pretreatment with injection clonidine is

equally a better alternative to lignocaine with similar advantages. This simple readily available method blunts the undesired hemodynamic side effects associated with laryngoscopy and intubation.

References

1. Reid LC, Brace DE. Irritation of the respiratory tract and its reflex effect upon heart. Surg Gynae Obstet. 1940;70:157-62.
2. Anila D. Malde, Vineet Sarode: Attenuation of the haemodynamic response to endotracheal intubation: Fentanyl Versus Lignocaine. The internet journal of anesthesiology. 2007;12(1).
3. Miller CD, Warren SJ. IV lignocaine fails to attenuate the cardiovascular response to laryngoscopy and tracheal intubation. Br J Anaesthesia. 1990;65:216.
4. Imani F, Alebouyeh MR, Taghipour Anvari Z, Faiz SH. Use of remifentanil and alfentanil in endotracheal intubation: a comparative study. Anesth Pain Med. 2011;1(2):61–5. doi: 10.5812/kowsar.22287523.2130.
5. Taghipour Anvari Z, Afshar-Fereydouniyan N, Imani F, Sakhaei M, Alijani B, Mohseni M. Effect of clonidine premedication on blood loss in spine surgery. Anesth Pain Med. 2012;1(4):252–6. doi: 10.5812/aapm.2197.
6. Shribman AJ, Smith G, Achola KJ. Cardiovascular and catecholamine responses to laryngoscopy with and without tracheal intubation. Br J Anaesth. 1987;59(3):295–9.
7. Sameenakousar M, Srinivasan KV. Comparison of fentanyl and clonidine for attenuation of the haemodynamic response to laryngocopy and endotracheal intubation. J Clin Diagn Res. 2013;7(1):106–11. doi: 10.7860/JCDR/2012/4988.2682.
8. Hassani V, Movassaghi G, Goodarzi V, Safari S. Comparison of fentanyl and fentanyl plus lidocaine on attenuation of hemodynamic responses to tracheal intubation in controlled hypertensive patients undergoing general anesthesia. Anesth Pain Med. 2013;2(3):115–8. doi: 10.5812/aapm.6442.
9. Kim WY, Lee YS, Ok SJ, Chang MS, Kim JH, Park YC, et al. Lidocaine does not prevent bispectral index increases in response to endotracheal intubation. Anesth.Analg. 2006;102(1):1569. doi:10.1213/01.ANE.0000184040.85956.98.
10. Aouad MT, Sayyid SS, Zalaket MI, Baraka AS. Intravenous lidocaine as adjuvant to sevoflurane anesthesia for endotracheal intubation in children. Anesth Analg. 2003;96(5):1325–7.
11. Tripathi DC, Shah KS, Dubey SR, Doshi SM, Raval PV. Hemodynamic stress response during laparoscopic cholecystectomy: Effect of two different doses of intravenous clonidine premedication. J Anaesthesiol Clin Pharmacol. 2011;27(4):475–80. doi: 10.4103/0970-9185.86586.
12. Ebneshahidi A, Mohseni M. Premedication with oral clonidine decreases intraoperative bleeding and provides hemodynamic stability in cesarean section. Anesth. Pain Med. 2011;1(1):30–3. doi: 10.5812/kowsar.22287523.1337.
13. Muzi M, Goff DR, Kampine JP, Roerig DL, Ebert TJ. Clonidine reduces sympathetic activity but maintains baroreflex responses in normotensive humans. Anesthesiology. 1992;77(5):864–71.
14. Pouttu J, Scheinin B, Rosenberg PH, Viinamaki O, Scheinin M. Oral premedication with clonidine: effects on stress responses during general anaesthesia. Acta Anaesthesiol Scand. 1987;31(8):730–4.
15. Quintin L, Roudot F, Roux C, Macquin I, Basmaciogullari A, Guyene T, et al. Effect of clonidine on the circulation and vasoactive hormones after aortic surgery. Br J Anaesth. 1991;66(1):108–15.
16. Byrd BF, Collins HW, Primm RK. Risk factors for severe bradycardia during oral clonidine therapy for hypertension. Arch Intern Med. 1988;148(3):729–33.
17. Idit Matot, J.Y. Sichel, Valeri Yofe and Yaacov Gozal: The effect of clonidine premedication on haemodynamic response to microlaryngoscopy and rigid bronchoscopy: Anesth Analg. 2000;91:828-33.
18. Davies DS, Wing LMH, Reid JL, et al. Pharmakokinetics and concentration-effect relationships of intravenous and oral clonidine. Clin Pharmacol Ther. 1977;21:593-601.
19. Routray SS, Raut K, Biswal D, Pradhan K, Mishra D. A Comparative Study of Fentanyl-Clonidine and Fentanyl-Lidocaine on Attenuation of Hemodynamic Stress Response to Laryngoscopy and Tracheal Intubation in Hypertensive Patients. 2014;4:27–31.
20. Kumari I, Naithni U, Bedi V, Gupta S,Gupta R, Bhuie. Comparison of clonidine versus midazolam in monitored anesthesia care during ENT surgery–A prospective, double blind, randomized clinical study. Anaesthesia, Pain and Intensive Care. 2012;16:157-64.

Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; (Part - II) 6(1): 353-357
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.49

A Comparative Study of Anaesthetic Efficacy of 0.75% Ropivacaine and 0.75% Ropivacaine with Dexmedetomidine in Epidural Anaesthesia for Inguinal Hernia Repair

B. Shakeela Begum[1], G. Narendren[2], N. Jothi[3]

[1]Assistant Professor [3]Professor, Department of Anaesthesiology, K.A.P. Viswanatham Government Medical College, Tirchirapalli, Tamil Nadu 620001, India, [2]Assistant Professor, Department of Anaesthesiology, Vinayaka Mission Medical College and Hospital, Karikal, Puducherry 609609, India.

Abstract

Introduction: Ropivacaine is nowadays replacing bupivacaine as the drug of choice in epidural anesthesia It has a high therapeutic index in a study conducted in humans.it is less neurotoxic and cardiotoxic than bupivacaine. One among the disadvantage in adding opioids is respiratory depression. To overcome this many studies emphasized adding clonidine with the local anesthetic drugas epidural anesthesia. This provides a marked reduction in the need for using hypnotics, inhaled opioids analgesics for treating postoperative pain. *Aim of the Study*: The clinical characteristics of epidural anesthesia performed with 0.75% ropivacaine and to evaluate the synergistic effect between dexmedetomidine and 0.75% ropivacaine in epidural anesthesia. *Materials and Methods*: After approval of the study by our institutional ethics committee, the study was conducted on 50 patients of both sexes, aged between 25 to 55 years and physical status according to the American Society of Anesthesiologists (ASA) Ior II, undergoin gelective inguinal hernia repair surgeries. Lumbar epidural anesthesia was performed to all the patients. Weight was ranging from 55-70 kg and height ranging from 150-172 cm. Group I: (n = 25): Patients received 1 ml of 0.9% normal saline + 19 ml of 0.75% hyperbaric ropivacaine. Group II: (n = 25): Patients received dexmedetomidine 1 µg /Kg + 0.9% normal saline so that total volume was completed to 1 ml + o.75% hyperbaric ropivacaine 19 ml was given. *Results*: The mean time required for the onset of sensory block Group –R 9.0800, Group-R Dex 8.0900 in both groups was not statistically significant. Group RDex achieved complete motor blockade (Bromage scale) much earlier than group R 22.8400 and Group-R Dex 19.0000 there was statistically significant difference noticed in between these two groups ('p' value < 0.05). Out of 25 patients, there are 2 in group-R and group- R Dex 5 had bradycardia with the heart rate of <55 beats /minute and it as treated with 0.3 mg of atropine. The sedation score between R and R Dex groups reveals a statistically significant difference (P<0.001). The side effects in both the groups were comparable; no statistical difference was noticed between the group-R and RDex. *Conclusion*: Present study obviously reveals that an apparent synergism between the two drugs namely dexmedetomidine and ropivacaine without any additional morbidity, which has been proved statistically significant using quantitative and qualitative analysis.

Keywords: Ropivacaine; Dexmedetomidine; Heart Rate; Blood Pressure.

How to cite this article:

B. Shakeela Begum, G. Narendren, N. Jothi. A Comparative Study of Anaesthetic Efficacy of 0.75% Ropivacaine and 0.75% Ropivacaine with Dexmedetomidine in Epidural Anaesthesia for Inguinal Hernia Repair. Indian J Anesth Analg. 2019;6(1):353-357.

Introduction

Epidural anesthesia is one of the central neuraxial blocks as well as versatile anesthetic technique, with many applications. Corning was the first man who described the epidural space in 1901 followed by epidural anesthesia was first used by Fidel Pages inhuman in the year 1921 and the in

Corresponding Author: G. Narendren, Assistant Professor, Department of Anaesthesiology, Vinayaka Mission Medical College and Hospital, Karikal, Puducherry 609609, India.

E-mail: dr.naren.md@gmail.com

Received on 23.10.2018, **Accepted on** 14.11.2018

1945 epidural needle was introduced by Tuohy, it is stillnow most commonly used needle for epidural anesthesia [1]. Epidural anesthesia became popular by the improvements in equipment; drugs. It has got many applications in various surgeries like obstetrics and pain control. It can be used as either a single injection technique or catheter technique [2]. This can be used as an anesthetic, as an analgesic adjuvant to general anesthesia, and it can be used for postoperative analgesia procedures involving thorax, abdomen, pelvis, perineum and lower limbs [3]. It also improves the postoperative outcome and attenuates the physiologic response to surgery, in particular, a significant reduction in pulmonary infections, pulmonary embolism, ileus, acute renal failure, and blood loss. Ropivacaine is nowadays replacing bupivacaine as the drug of choice in epidural anesthesia. It shows the high therapeutic index in humans. It is less neurotoxic and cardiotoxic than bupivacaine. Various drugs like α_2 adrenergic agonists, opioid, ketamine, midazolam, magnesium sulfate, adrenaline have been added along with local anesthetics in epidural anesthesia to improve the duration and quality of analgesia [4]. One among the disadvantage in adding opioids is respiratory depression. To overcome this many studies emphasized adding clonidine with the localanesthetic drug as epidural anesthesia [5]. This provides a marked reduction in the need for using hypnotics, inhaled opioids analgesics for treating postoperative pain. In animal models, studies were conducted using clonidine, dexmedetomidine as adjuvant drugs in epidural anesthesia to prolong its effect thereby reducing the need for opioids [6]. In humans, in the year 1997, the dexmedetomidine was administered epidurally by adding with lignocaine 1.5% in patients undergoing hysterectomy, to prolong the postoperative analgesia. Compared with clonidine, dexmedetomidine is an α_2-adrenergic agonist with high selectivity ratio between α_2 and α1 (1620:1), seven to ten times more selective for α_2 receptor and has got the shorter duration of action [7]. Because its sedative, analgesic and sympatholytic activity it is being used widely in critical care. There have been only fewer studies in the perioperative effect of epidural dexmedetomidine [8].

Materials and Methods

A randomized double-blind controlled study was conducted in 50 patients undergoing inguinal hernia surgeries in KAPV Govt medical college hospital. After getting institutional ethical committee approval, the procedure was explained to the patients in detail. Informed valid consent was obtained from all patients who are included in the study and they randomly allocated into two groups, 25 in each group. Group R (n=25) = patients receiving 0.75% Ropivacaine (hyperbaric) 19 ml +1 ml of 0.9% normal saline. Group RDex (n=25)= patients receiving Dexmedetomidine 1 μg/kg +0.9% of normal saline so that total volume was completed to 1 ml along with 0.75% Ropivacaine (hyperbaric) 19 ml.

Selection Criteria: Patient selected for the study are male gender between the age group of 25 -55 years with ASA I and ASA II physical status scheduled for elective inguinal hernia repair under epidural anesthesia.

Inclusion Criteria:

1. ASA grade I & II status
2. Male gender
3. 25 -55 years of age
4. Patients giving informed written consent.
5. Patients scheduled to undergo elective inguinal hernia repair under epidural anesthesia.

Exclusion Criteria

1. ASA III or greater
2. Age more than 55 years, and less than 25 years
3. Patients with known h/o allergy to local anesthetic drugs
4. Uncooperative patients with hypotension, previous spinal surgeries, spine abnormalities, local site infection and coagulation abnormalities
5. Poorly controlled hypertension, angina, cardiopulmonary disease
6. Patients with hematological disease, neurologic, psychiatric disease, severe renal or hepatic derangement
7. Patients taking tricyclic antidepressants, any antipsychotic drugs, alpha-2 adrenergic agonists, opioids, anti-arrhythmic, beta blockers, and anticoagulants.

Procedure

In the operation theatre a good intravenous line secured with 18 G cannula to administer Ringer's lactate, 8 ml/Kg/hr as a preloading solution. Baseline pulse rates, blood pressure, SpO_2, ECG

were recorded. The patient was placed in the Rt lateral position. Under aseptic precaution skin over L3-L4 space infiltrated with 2 ml of 2% lignocaine. 17G Tuohy needle was introduced at L3-L4 interspace through the midline approach, entry of the needle into epidural space is confirmed using the loss of resistance technique. After negative aspiration for blood and CSF, 3 ml of 2% lignocaine with adrenaline 1 in 200000 dilutions was given into epidural space as a test dose. After 5–7 minutes of observation for effects of intravascular or intrathecal injection (like change in pulse rate, unable to dorsiflex great toe), Group-R received 20 mL of 0.75% ropivacaine, whereas Group-Rdex received 20 mL of 0.75% ropivacaine and dexmedetomidine 1 μg/ kg epidurally at a rate of 1 ml per 3 second. Time of administration of the drug is noted.

Results

Table 1: Showing Demographic Profile of Patients in Both Groups

Patient's Profile	Group-R (Mean± SD)	Group-R Dex (Mean±SD)	p value > 0.05 Not Significant
Age in years (25-55)	42.76±9.85	39.32±9.11	0.155
Weight in Kg (50-70)	58.46±5.25	61.24±6.83	0.21
Height in Cm (156 -172)	160.36±7.27	158.28±6.64	0.303

The 50 patients were involved in this study, and they randomly allocated into two groups namely R & RDex consisting of 25 patients in each group. The demographic profile regarding age, height, and weight were comparable in both R and RDex groups and did not show any significant statistical difference (Table 1).

Table 2: Showing Onset of Sensory Block of Patients (in min.)

The onset of sensory block (min.)at T 10	Group-R	Group-RDex
Mean	9.0800	8.0900
S.D	0.75939	0.65940
'p'	0.1000 Not Significant	

The mean time required for the onset of sensory block Group –R 9.0800, Group-RDex 8.0900 in both groups was not statistically significant. Group RDex achieved complete motor blockade (Bromage scale) much earlier than group R 22.8400 and Group-RDex 19.0000 there was statistically significant difference noticed in between these two groups ('p' value < 0.05) (Table 2).

Table 3: Showing time Taken for Complete Motor Block (in min.)

The onset of motor block (min.)	Group-R	Group-RDex
Mean	22.8400	19.0000
S.D	3.77200	3.93649
'p'	0.033 Significant	

Group RDex achieved complete motor blockade (Bromage scale) much earlier than group R 22.8400 and Group-RDex 19.0000 there was statistically significant difference noticed in between these two groups ('p' value < 0.05) (Table 3).

Table 4: Showing the Duration of Sensory Block (in hrs.)

Duration of sensory (hrs.)	Group-R	Group-RDex
Mean	2.7600	6.8400
S.D	0.43589	0.68799
'p'	0.001 Significant	

Meantime of postoperative analgesia in group-RDex (6.8400) was significantly higher than group-R (2.7600) and statistically significant ('p' value < 0.05) (Table 4).

Table 5: Showing the Pulse Rate of Patients in Both the Groups

Sl. No.	Pulse	Group-R Mean± SD	Group-RDex Mean± SD	'p' value
1.	0 min	83.8400±11.01393	81.1600±10.14347	0.375
2.	2 mins.	83.9600±9.91833	78.6400±9.66902	0.061
3.	5 mins. 80.4000±8.13941		75.9600±10.54546	0.102
4.	10 mins.	78.2400±8.23752	73.6000±9.03696	0.064
5.	15 mins.	78.5200±9.38580	71.0400±8.61916	0.117
6.	30 mins.	78.7600±8.30803	70.8800±9.36447	0.145
7.	60 mins.	78.0400±8.56582	72.2000±9.74679	0.059
8.	120 mins.	78.3200±8.59612	72.8800±9.66230	0.061
9.	180 mins.	78.2400±9.12086	75.1600±9.58158	0.250

Pulse rate variables in both the groups were comparable in both the groups. After the 15th minute in RDex group, there was a slight fall in pulse rate but it was not statistically significant. This can be possible due to the effect of dexmedetomidine. The decrease in the heart rate remained up to 2 hours. The heart rate remained stable without any fluctuation in either of the groups which is statistically not significant (P> 0.05). Out of 25 patients, there are 2 in group-R and group- RDex 5 had bradycardia with the heart rate of <55 beats /minute and it as treated with 0.3 mg of atropine (Table 5).

Table 6: Showing Sedation Score of Patients in both the Groups

Sedation score	Group-R		Group-RDex	
	n	%	n	%
0	16	64.0	1	4
1	6	24.0	7	28
2	2	8	13	52.0
3	1	4	3	12.0
4	0	0	1	4
5	0	0	0	0
Total	25	100	25	100
Mean	1.4800		3.4800	
SD	0.50222		0.40490	
'p'	0.001 Significant			

It reveals a statistically significant difference ($p<0.001$). The side effects in both the groups were comparable; no statistical difference was noticed between the group-R and RDex (Table 6).

Table 7: Showing the two Segment Regression time (in min.)

Two segment regression time (min.)	Group-R	Group-RDex
Mean	118.2800	167.0000
SD	5.36594	43.62912
'p'	0.001 Significant	

IT reveals that the two regression time was prolonged in group-RDex than group-R, statistically significant difference was noticed ('p' value < 0.05) (Table 7).

Discussion

In this study, the hypothesis that dexmedetomidine enhances the clinical effects of the ropivacaine on epidural administration without altering the hemodynamics was evaluated [9]. According to the results obtained from the present study, there is a definite synergistic interaction between ropivacaine and dexmedetomidine drugs [10]. Many studies have been published in national and international journals regarding the use of any local anesthetics along with dexmedetomidine for epidural anesthesia in humans by analyzing the time of onset of the epidural block and its duration [11]. In the present study, it was observed that there was no significant difference between the ropivacaine group (R) as control and ropivacaine plus dexmedetomidine (RDex) as a study group. Results obtained from our study regarding onset of sensory block in dermatomes T10, T12 and T8 are closely correlated with the study made by Li X, Eisenach et al. by administering clonidine 150 mg or dexmedetomidine 100 µg with 1% ropivacaine and they also found that there was no significance in the onset of sensory block using the above drugs in their study [12]. The administration of dexmedetomidine with ropivacaine also increases the duration of sensory block in dermatome T10 and T12 significantly. In addition, a significant increase in the duration of sensory block was noticed in our study by adding dexmedetomidine 1 microgram per kg along with 0.75% of ropivacaine [13]. Our study is also supported by Silva et al., 2002. He also found that the postoperative analgesia was increased when adding dexmedetomidine 2 µg/Kg with 0.5% bupivacaine for epidural anesthesia in patients undergoing a hysterectomy. Our results regarding the onset of sensory block and duration of the sensory block are similar with reports made by Hogue CW et al. They studied the synergistic effect of dexmedetomidine 1 µg /Kg with 0.75% ropivacaine in orthopedic surgeries [14]. In our study, the maximum level of sensory blockade was comparable and it was T4 in both groups. There was no statistical difference observed. This finding correlates with the study of Fukushima Ket al (1995) [15]. In their study, 20 ml volume of 0.75% ropivacaine and 0.5% bupivacaine were used for epidural anesthesia and it was found that the maximum cephalad spread was T4. In this study, the assessment of motor blockade was performed before surgery using modified Bromage scale and the time to achieve complete motor blockade was significantly earlier in the (19.0±3.94) patients who have received dexmedetomidine (group-RDex) as compared to group-R (22.84±3.78). ($p=0.033$), this finding correlates with the results of the study by which evaluate effects of adding dexmedetomidine (1 µg/Kg) with 0.75% ropivacaine (15 ml) (RD- group) comparing with that of 0.75% ropivacaine with fentanyl 1 µg/kg (RF) in epidural anesthesia in lower limb orthopedic surgeries. In that study time to complete motor blockade is much [16]. In our study, hemodynamic parameters were comparable between both groups during the intraoperative and postoperative period. In RDex group a fall in pulse rate was observed comparatively. But there was no significant intergroup variation. Likewise, fall in systolic blood pressure noticed in RDex group but it was not below the level of the baseline and did not require any active treatment. Diastolic pressure was stable and it was stable and comparable between both groups without any statistically significant difference [17]. Kalso EA, et al. studied the synergistic effect of dexmedetomidine with ropivacaine without any morbidity and hemodynamic instability due to drug association [18]. The intensity of

bradycardia and fall in blood pressure after the epidural administration of dexmedetomidine is dependenton the dose, as well as the spinal level where the drug[1] is injected. Thus, higher doses and the thoracic level administration may increase the occurrence of these hemodynamic events. [19] Douglas AG, et al. studied the highest incidence of bradycardia in patients receiving dexmedetomidine in higher dosage like 2 µg/Kg [20].

Conclusion

We conclude that ropivacaine 0.75% with dexmedetomidine 1 µg /Kg in epidural anesthesia has good anesthetic efficacy, increases the duration of postoperative analgesia without significant variation in hemodynamic or any additional morbidity; when compared to plain ropivacaine 0.75%.

References

1. Rajaraman J and Shanmugam P.S. Effect of dexmedetomidine as an adjuvant to epidural ropivacaine 0.75%. PPT presentation of Anaesthesiology Department, Kilpauk Medical College, Chennai. 2010;1-36.
2. Bajwa SJ et al., Dexmedetomidine and clonidine in epidural anesthesia: A comparative evaluation. Indian J Anaesth. 2011;55:116-21.
3. Milligan KR, et al., The efficacy and safety of epidural infusions of levobupivacaine with or without clonidine for postoperative pain relief in patients undergoing total hip replacement. Anesth Analg. 2000;91:393-97.
4. Vieira AM, et al., Epidural clonidine or dexmedetomidine for post-cholecystectomy analgesia and sedation. Rev Bras Anestesiol. 2004; 54(4):473-78.
5. El-Hannaway AM, et al., Addition of dexmedetomidine prolongs caudal analgesia in children. Br J Anaesth. 2009;103(2):268-74.
6. Oriol-lopez SA, et al., Epidural dexmedetomidine in regional anaesthesia to reduce anxiety. Revista Mexicana de Anaestesiologia. 2008;31(4):271-77.
7. Syal K, et al., Epidural labour analgesia using bupivacaine and clonidine. J AnaesthClinPharmacol 2011;27(1):87-90.
8. Aveline C, et al., The effect of clonidine on the minimum local analgesic concentration of epidural ropivacaine during labor. AnesthAnalg. 2002;95:735-40.
9. Landau R, Schiffer E, Morales M, Savoldelli G, Kern C. The dose-sparing effect of clonidine added to ropivacaine for labor epidural analgesia. AnesthAnalg. 2002;95:728-34.
10. McClure JH, Ropivacaine (Review article). British Journal of Anaesthesia. 1996;76:300-307.
11. Bonnet F, et al., Postoperative analgesia with extradural clonidine. Br.J. Anaesth. 1989;63(4): 465-469.
12. Li X, Eisenach J. Alpha 2 adrenoreceptor stimulation reduces capsaicin-induced glutamate release from spinal cord synaptosomes. J PharmacolExpTher. 2001;299(3);939-44.
13. Fukushima K, et al., The effect of epidurally administered dexmedetomidine on central and peripheral nervous system in man. AnaesthAnalg. 1997;84;S292.
14. Hogue CW. Autonomic nervous system responses during sedative infusions of dexmedetomidine. Anesthesiology. 2002;97(3):592-598.
15. Fukushima K, Nishimi Y, Mori K, Kaneko I, Fukushima Y. Effect of epidurally administered dexmedetomidine on sympathetic activity and postoperative pain in man. AnesthAnalg. 1996; 82:S121.
16. Maze M and Regan JW. Role of signal transduction in anesthetic action: alpha 2 adrenergic agonists. Ann NY Acad Sci. 1991;625:409-422.
17. Memis D et al., Adding dexmedetomidine to lidocaine for intravenous regional anesthesia. AnaesthAnalg. 2004;98(3):835-840.
18. Kalso EA, et al., Spinal anticiceptors by dexmedetomidine, a highly selective alpha 2 agonists. PharmacolToxicol. 1991;68(2):140-43.
19. Jackal ML, et al., The analgesic action of dexmedetomidine: a novel alpha 2 adrenoceptor agonist in healthy volunteers. Pain. 1991;46(3): 281-85.
20. Douglas AG, et al., Dexmedetomidine and meperidine additively reduce the shivering threshold in humans. Stroke. 2003 May;34(5):1218-23.
21. Klimscha W et al., Hemodynamic and analgesic effects of clonidine added repetitively to the continuous epidural and spinal blocks. AnesthAnalg. 1995;80:322-7.

Case Report

Indian Journal of Anesthesia and Analgesia
2019; 6(1) (Part - II): 359-361
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.50

Low Back Pain with Radiculopathy in a Patient due to Herniated Disc and Associated Cerebellar Ataxia

Rachna Varma[1], Minal Chandra[2], Sudheer Dara[3]

[1]Chief Consultant Pain Physician, Medical Director, Epione Centre of Pain Relief and beyond Varma Union Hospital, Indore, Madhya Pradesh 452002, India. [2]Consultant Pain Physician, Epione Centre of pain Relief and Beyond Jubilee Hills, Hyderabad, Hyderabad, Telangana 500033, India. [3]Chief and Director of Pain Medicine, Continental Hospitals, Hyderabad, Telangana 500035, India.

Abstract

Low back pain with radiating pain, tingling or numbness in lower limbs is most commonly due to prolapsed and herniated intervertebral disc. The pain is neuropathic and usually increases with walking. We report a patient with severe back pain with radiculopathy of one monthduration in a patient with cerebellar ataxia for 30 years with increasing unsteadiness of gait for last 30 years.

Keywords: low Back pain; radiculopathy; prolapsed intervertebral disc; cerebellar ataxia.

How to cite this article:

Rachna Varma, Minal Chandra, Sudheer Dara. Low Back Pain with Radiculopathy in a Patient due to Herniated Disc and Associated Cerebellar Ataxia. Indian J Anesth Analg. 2019;6(1):359-361.

Introduction

Low Back pain with radiculopathy is commonly caused by a prolapsed or herniated intervertebral disc (PIVD) The presence and location of pain, paraesthesia and other symptoms depend on the site and degree of prolapse. The common intervertebral disc (IVD) involved are the L4-5 and L5-S1 as they are in line of weight bearing axis. PIVD is herniated nucleus pulposus where it is displaced beyond the edges of vertebral ring apophyses. Patient presents with low back pain with radiculopathy, motor or sensory deficits according to the level of compression of the nerve root. Motor deficit if present is considered to be a red flag and is an indication for surgical intervention. Cerebellar ataxia can occur as a result of damage to cerebellum and can occur due to many diseases in cerebellum. The patients present with symptoms of unsteadiness of gait, inability to coordinate balance, speaking disability and eye movements. We present a case report of a patient with back pain with radiculopathy for 2 months with cerebellar ataxia because of Arnold Chiari Malformation for which she was operated in 1997 but had gradual increase in unsteadiness of gait and balance. She walks with the support of walker.

Case report

A 58 years old female patient presented with low back pain radiating to both lower limbs more in right lower limb till foot and till knee joint in

Corresponding Author: Rachna Varma, Chief Consultant Pain Physician, Medical Director, Epione Centre of Pain Relief and beyond Varma Union Hospital, Indore, Madhya Pradesh 452002, India.

E-mail: varuny.indore09@gmail.com

Received on 29.11.2018, **Accepted on** 10.12.2018

left lower limb of 1 month duration. The pain increased on walking and decreased on resting. She was a case of cerebellar ataxia because of Arnold Chiari Malformation for which she was surgically treated in 1997 and since then she had problems in balancing and gait difficulty and slurring of speech. She walked with a support of walker. On examination she appeared to be in extreme agony and restless. Straight leg raising test (Lasegue's test) was positive at 90 degrees, Fabers or Patrick test was positive on right side. Tenderness present in midline lumbar spine and right posterior superior iliac spine. There was no motor deficit. Decreased sensation to touch was present in lower lumbar dermatomes. Muscle Tone and deep tendon reflexes were normal. Cerebellar signs like finger nose test, knee heel test were positive. Nystagmus was present. Cranial nerve examinations were normal. She had no involuntary movements or tremors. Her visual analogue score VAS was 8/10 She was advised MRI lumbar spine. MRI showed L4-L5 intervertebral disc herniation with large bulging component towards left along with ligamentum flavum hypertrophy and facetal hypertrophy causing bilateral neural foraminal stenosis. Mild degenerative spondylotic changes are present in multiple lumbar level. Patient had been advised endoscopic discectomy but had refused. The patient and attendants were counselled and explained the prognosis of surgical and non surgical interventions. An explained informed consent was taken. Patient was shifted to OT. With all resuscitative measures and monitors in place. An 18 G intravenous catheter was inserted. Patient was put in prone position and the back was cleaned and draped and a C -Arm was put in position. A L4 right and left nerve root block by transforaminal approach and a L5 -S1 interlaminar epidural block with triamcinolone 40 mg and 0.25% of bupivicaine was done under local anaesthesia and fluoroscopy. The patient was stable throughout the procedure and post procedure. Her pain scores decreased and post procedure VAS was 0/10. She was observed for 2 hours and sent home with analgesics, antineuropathics and was advised physiotherapy. She was followed up after 5 days and then at monthly intervals. She was found to be pain free and comfortable and no worsening of neurological symptoms were found at subsequent follow up.

Discussion

PIVD is the most common cause of pain and radiculopathy. The presence of pain and other symptoms depend on the site and degree of prolapse. PIVD is most common at L4-5 and L5-S1. Most patient recover within few weeks but in some patient the symptoms progress leading to complications like paraesthesia, numbness, weakness of limbs, cauda equina syndrome, bladder and bowel problems. A disc prolapse involves the displacement of nuclear material. In the lumbar spine it is most common between ages of 30 to 50 years. Both mechanical and biochemical degenerative changes are involved in mechanics of disc prolapse. It is important to understand the natural history of prolapsed disc, including history of trauma. Medical history should be taken to rule out infection, malignancy or other systemic illness like Diabetes. Proper physical examinations should be done. Specific provocative tests for PIVD with radiculopathy are Straight leg raising test (SLR, Lasegue's test), Well- leg raising test (cross-over Lasegue's test), Slump test, Prone knee bend test (for L3 and L4 root). Palpation should be done to look for tenderness on spine, paraspinal muscles and sacroiliac joints.

Identification of red flags like motor deficit, bladder or bowel involvement, meningeal involvement are of utmost importance in treatment of patients. In patients with rapidly progressing motor weakness surgery should be choice of treatment. Proper selection of patient for conservative treatment is important and should be first choice in patients with pain with radicular pain. Diagnosis of PIVD is done by MRI. Saggital and axial view can show the degree and site of prolapse. The differential diagnosis for back pain with or without radiculopathy is SI joint pain, facetal pain, Piriformis syndrome, myofacial pain.

Chiari Malformation types (1-4) is a spectrum of developmental anomaly of hind brain. It affects the structural relationship between the cerebellum, brain stem, the upper cervical cord and the bony cranial base. Arnold Chiari Malformation is type 2 variety. There is anomaly of herniation of cerebellar tonsils through foramen magnum producing compression of cervicomedullary junction. It presents with signs and symptoms of cerebellar dysfunction like ataxia,dysarthria, dysphagia, nystagmus and dissociative sensory loss. Natural history of patient remains unclear where in they remain stable or may deteriorate over years. This patient was operated in 1997 where in she underwent foramen magnum decompression and Duraplasty. She had gradual increase in unsteadiness of gait and balance so that she required a walking support. After thorough neurological examinations and identification of the current pathological conditions plan was made to give bilateral L4 transforaminal injection under day care.

Conclusion

Low back pain is a very common condition and a patient presenting with low back pain with radiculopathy should be assessed thoroughly with proper history taking, local and general examinations, neurological examinations, imaging, identification of red flags and then appropriate decision for surgical or non surgical intervention should be taken. Any preexisting neurological conditions make it complex and should be very carefully approached to prevent complications and reach a proper diagnosis.

Financial support and sponsorship: Nil

Conflicts of interest: There are no conflicts of interest.

References

1. Bogduk. The anatomical basis for spinal pain syndromes. J Manipulative Physiology therapy. 1995;18:603-05.
2. Bogduk N. Nerves of lumbar spine. In clinical anatomy of the lumbar spine and sacrum. Churchill Livingstone; New York. 1997.pp.127-44.
3. Bogduk N. Low back pain Churchill Livingstone 1997.pp.187-213.
4. Derby R, Kine G, Saal JA et al. Response to steroid and duration of radicular pain as predictors of surgical outcome. Spine. 1992;17 Suppl;176-83.
5. Balaji VR, Chin KF, Tucker S, Wilson LF, Casey AT. Recovery of severe motor deficit secondary to herniated disc prolapse. Is surgical intervention important? a systemic review. Eur Spine J. 2014 Sep;23(9):1968-77.
6. Humphreys SC, Eck JC. Clinical evaluation and treatment options for herniated Lumbar disc. Am Fam Physician. 1999 Feb 1;59(3):575-82, 587-8.
7. Kanal S Paul. Arnold Chiari Malformation -Review of 71 cases. J neurosurgery. 1983;58:183–87.
8. Mohr PD, Strang FA, Sambrook MA et al. The clinical and surgical seizures in 40 patients with primary Cerebellar Ectopia QJ Med. 1997;46;85-96.

Guidelines for Authors

Manuscripts must be prepared in accordance with "Uniform requirements for Manuscripts submitted to Biomedical Journal" developed by international committee of medical Journal Editors

Types of Manuscripts and Limits

Original articles: Up to 3000 words excluding references and abstract and up to 10 references.

Review articles: Up to 2500 words excluding references and abstract and up to 10 references.

Case reports: Up to 1000 words excluding references and abstract and up to 10 references.

Online Submission of the Manuscripts

Articles can also be submitted online from http://rfppl.co.in/customer_index.php.

I) First Page File: Prepare the title page, covering letter, acknowledgement, etc. using a word processor program. All information which can reveal your identity should be here. use text/rtf/doc/PDF files. Do not zip the files.

2) Article file: The main text of the article, beginning from Abstract till References (including tables) should be in this file. Do not include any information (such as acknowledgement, your name in page headers, etc.) in this file. Use text/rtf/doc/PDF files. Do not zip the files. Limit the file size to 400 Kb. Do not incorporate images in the file. If file size is large, graphs can be submitted as images separately without incorporating them in the article file to reduce the size of the file.

3) Images: Submit good quality color images. Each image should be less than 100 Kb in size. Size of the image can be reduced by decreasing the actual height and width of the images (keep up to 400 pixels or 3 inches). All image formats (jpeg, tiff, gif, bmp, png, eps etc.) are acceptable; jpeg is most suitable.

Legends: Legends for the figures/images should be included at the end of the article file.

If the manuscript is submitted online, the contributors' form and copyright transfer form has to be submitted in original with the signatures of all the contributors within two weeks from submission. Hard copies of the images (3 sets), for articles submitted online, should be sent to the journal office at the time of submission of a revised manuscript. Editorial office: Red Flower Publication Pvt. Ltd., 48/41-42, DSIDC, Pocket-II, Mayur Vihar Phase-I, Delhi – 110 091, India, Phone: 91-11-22754205, 45796900, 22756995. E-mail: author@rfppl.co.in. Submission page: http://rfppl.co.in/article_submission_system.php?mid=5.

Preparation of the Manuscript

The text of observational and experimental articles should be divided into sections with the headings: Introduction, Methods, Results, Discussion, References, Tables, Figures, Figure legends, and Acknowledgment. Do not make subheadings in these sections.

Title Page

The title page should carry

1) Type of manuscript (e.g. Original article, Review article, Case Report)

2) The title of the article, should be concise and informative;

3) Running title or short title not more than 50 characters;

4) The name by which each contributor is known (Last name, First name and initials of middle name), with his or her highest academic degree(s) and institutional affiliation;

5) The name of the department(s) and institution(s) to which the work should be attributed;

6) The name, address, phone numbers, facsimile numbers and e-mail address of the contributor responsible for correspondence about the manuscript; should be mentoined.

7) The total number of pages, total number of photographs and word counts separately for abstract and for the text (excluding the references and abstract);

8) Source(s) of support in the form of grants, equipment, drugs, or all of these;

9) Acknowledgement, if any; and

l0) If the manuscript was presented as part at a meeting, the organization, place, and exact date on which it was read.

Abstract Page

The second page should carry the full title of the manuscript and an abstract (of no more than 150 words for case reports, brief reports and 250 words for original articles). The abstract should be structured and state the Context (Background), Aims, Settings and Design, Methods and Materials, Statistical analysis used, Results and Conclusions. Below the abstract should provide 3 to 10 keywords.

Introduction

State the background of the study and purpose of the study and summarize the rationale for the study or observation.

Methods

The methods section should include only information that was available at the time the plan or protocol for the study was written such as study approach, design, type of sample, sample size, sampling technique, setting of the study, description of data collection tools and methods; all information obtained during the conduct of the study belongs in the Results section.

Reports of randomized clinical trials should be based on the CONSORT Statement (http:// www. consort-statement. org). When reporting experiments on human subjects, indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2000 (available at http://www.wma. net/e/policy/l 7-c_e.html).

Results

Present your results in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat in the text all the data in the tables or illustrations; emphasize or summarize only important observations. Extra or supplementary materials and technical details can be placed in an appendix where it will be accessible but will not interrupt the flow of the text; alternatively, it can be published only in the electronic version of the journal.

Discussion

Include summary of key findings (primary outcome measures, secondary outcome measures, results as they relate to a prior hypothesis); Strengths and limitations of the study (study question, study design, data collection, analysis and interpretation); Interpretation and implications in the context of the totality of evidence (is there a systematic review to refer to, if not, could one be reasonably done here and now?, What this study adds to the available evidence, effects on patient care and health policy, possible mechanisms)? Controversies raised by this study; and Future research directions (for this particular research collaboration, underlying mechanisms, clinical research). Do not repeat in detail data or other material given in the Introduction or the Results section.

References

List references in alphabetical order. Each listed reference should be cited in text (not in alphabetic order), and each text citation should be listed in the References section. Identify references in text, tables, and legends by Arabic numerals in square bracket (e.g. [10]). Please refer to ICMJE Guidelines (http://www.nlm.nih.gov/bsd/uniform_ requirements.html) for more examples.

Standard journal article

[1] Flink H, Tegelberg Å, Thörn M, Lagerlöf F. Effect of oral iron supplementation on unstimulated salivary flow rate: A randomized, double-blind, placebo-controlled trial. J Oral Pathol Med 2006; 35: 540-7.

[2] Twetman S, Axelsson S, Dahlgren H, Holm AK, Källestål C, Lagerlöf F, et al. Caries-preventive effect of fluoride toothpaste: A systematic review. Acta Odontol Scand 2003; 61: 347-55.

Article in supplement or special issue

[3] Fleischer W, Reimer K. Povidone iodine antisepsis. State of the art. Dermatology 1997; 195 Suppl 2: 3-9.

Corporate (collective) author

[4] American Academy of Periodontology. Sonic and ultrasonic scalers in periodontics. J Periodontol 2000; 71: 1792-801.

Unpublished article

[5] Garoushi S, Lassila LV, Tezvergil A, Vallittu PK. Static and fatigue compression test for particulate filler composite resin with fiber-reinforced composite substructure. Dent Mater 2006.

Personal author(s)

[6] Hosmer D, Lemeshow S. Applied logistic regression, 2nd edn. New York: Wiley-Interscience; 2000.

Chapter in book

[7] Nauntofte B, Tenovuo J, Lagerlöf F. Secretion and composition of saliva. In: Fejerskov O,

Kidd EAM, editors. Dental caries: The disease and its clinical management. Oxford: Blackwell Munksgaard; 2003. p. 7-27.

No author given

[8] World Health Organization. Oral health surveys - basic methods, 4th edn. Geneva: World Health Organization; 1997.

Reference from electronic media

[9] National Statistics Online—Trends in suicide by method in England and Wales, 1979-2001. www.statistics.gov.uk/downloads/theme_health/HSQ20.pdf (accessed Jan 24, 2005): 7-18. Only verified references against the original documents should be cited. Authors are responsible for the accuracy and completeness of their references and for correct text citation. The number of reference should be kept limited to 20 in case of major communications and 10 for short communications.

More information about other reference types is available at www.nlm.nih.gov/bsd/uniform_requirements.html, but observes some minor deviations (no full stop after journal title, no issue or date after volume, etc).

Tables

Tables should be self-explanatory and should not duplicate textual material.

Tables with more than 10 columns and 25 rows are not acceptable.

Table numbers should be in Arabic numerals, consecutively in the order of their first citation in the text and supply a brief title for each.

Explain in footnotes all non-standard abbreviations that are used in each table.

For footnotes use the following symbols, in this sequence: *, ¶, †, ‡‡,

Illustrations (Figures)

Graphics files are welcome if supplied as Tiff, EPS, or PowerPoint files of minimum 1200x1600 pixel size. The minimum line weight for line art is 0.5 point for optimal printing.

When possible, please place symbol legends below the figure instead of to the side.

Original color figures can be printed in color at the editor's and publisher's discretion provided the author agrees to pay.

Type or print out legends (maximum 40 words, excluding the credit line) for illustrations using double spacing, with Arabic numerals corresponding to the illustrations.

Sending a revised manuscript

While submitting a revised manuscript, contributors are requested to include, along with single copy of the final revised manuscript, a photocopy of the revised manuscript with the changes underlined in red and copy of the comments with the point to point clarification to each comment. The manuscript number should be written on each of these documents. If the manuscript is submitted online, the contributors' form and copyright transfer form has to be submitted in original with the signatures of all the contributors within two weeks of submission. Hard copies of images should be sent to the office of the journal. There is no need to send printed manuscript for articles submitted online.

Reprints

Journal provides no free printed reprints, however a author copy is sent to the main author and additional copies are available on payment (ask to the journal office).

Copyrights

Declaration

A declaration should be submitted stating that the manuscript represents valid work and that neither this manuscript nor one with substantially similar content under the present authorship has been published or is being considered for publication elsewhere and the authorship of this article will not be contested by any one whose name (s) is/are not listed here, and that the order of authorship as placed in the manuscript is final and accepted by the co-authors. Declarations should be signed by all the authors in the order in which they are mentioned in the original manuscript. Matters appearing in the Journal are covered by copyright but no objection will be made to their reproduction provided permission is obtained from the Editor prior to publication and due acknowledgment of the source is made.

Approval of Ethics Committee

We need the Ethics committee approval letter from an Institutional ethical committee (IEC) or an institutional review board (IRB) to publish your Research article or author should submit a statement that the study does not require ethics approval along with evidence. The evidence could either be consent from patients is available and there are no ethics issues in the paper or a letter from an IRB stating that the study in question does not require ethics approval.

Abbreviations

Standard abbreviations should be used and be spelt out when first used in the text. Abbreviations should not be used in the title or abstract.

Checklist

- Manuscript Title
- Covering letter: Signed by all contributors
- Previous publication/ presentations mentioned, Source of funding mentioned
- Conflicts of interest disclosed

Authors

- Middle name initials provided.
- Author for correspondence, with e-mail address provided.
- Number of contributors restricted as per the instructions.
- Identity not revealed in paper except title page (e.g.name of the institute in Methods, citing previous study as 'our study')

Presentation and Format

- Double spacing
- Margins 2.5 cm from all four sides
- Title page contains all the desired information. Running title provided (not more than 50 characters)
- Abstract page contains the full title of the manuscript
- Abstract provided: Structured abstract provided for an original article.
- Key words provided (three or more)
- Introduction of 75-100 words
- Headings in title case (not ALL CAPITALS).
  References cited in square brackets
- References according to the journal's instructions

Language and grammar

- Uniformly American English
- Abbreviations spelt out in full for the first time. Numerals from 1 to l0 spelt out
- Numerals at the beginning of the sentence spelt out

Tables and figures

- No repetition of data in tables and graphs and in text.
- Actual numbers from which graphs drawn, provided.
- Figures necessary and of good quality (color)
- Table and figure numbers in Arabic letters (not Roman).
- Labels pasted on back of the photographs (no names written)
- Figure legends provided (not more than 40 words)
- Patients' privacy maintained, (if not permission taken)
- Credit note for borrowed figures/tables provided
- Manuscript provided on a CDROM (with double spacing)

Submitting the Manuscript

- Is the journal editor's contact information current?
- Is the cover letter included with the manuscript? Does the letter:

1. Include the author's postal address, e-mail address, telephone number, and fax number for future correspondence?
2. State that the manuscript is original, not previously published, and not under concurrent consideration elsewhere?
3. Inform the journal editor of the existence of any similar published manuscripts written by the author?
4. Mention any supplemental material you are submitting for the online version of your article. Contributors' Form (to be modified as applicable and one signed copy attached with the manuscript)