Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(5) (Part - II): 1731-1736
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6519.34

Magnesium Sulphate with and without Clonidine as Adjuvant to Bupivacaine for Lower Abdominal Surgeries: A Randomized Clinical Trial

Archana Amol Gautam[1], Vishnu Madhusoodanan[2]

[1]Assistant Professor, [2]Resident, Department of Anesthesia, Krishna Institute of Medical Sciences, Malkapur, Karad (Dist. Satara), Maharashtra 415539, India.

Abstract

Background: Postoperative pain relief is a growing concern for an anesthesiologist as an uneventful postoperative period makes surgery a comfortable proposition for surgical patients. *Objectives:* To assess the duration of effective analgesia. To assess hemodynamic parameters during the surgery and to determine any adverse effects if any. *Methods:* A prospective randomized controlled trial was done in patients posted for elective lower abdominal and lower limb surgeries for 2 years. Two groups were decided Group M (n=35), received 3 ml of 0.5% hyperbaric bupivacaine, preservative free magnesium sulfate 50%, 0.1 ml (50 mg) and preservative free normal saline 0.5 ml. Group CM (n=35), received 3 ml of 0.5% hyperbaric bupivacaine, preservative free magnesium sulfate 50%, 0.1 ml (50 mg) and clonidine 0.5 ml (75 µg). SPSS (version 22.0) was used for analysis. *Results:* Most of the patients belonged to age group between 41–50 years in both the groups. The duration (minutes) of analgesia was prolonged in Group CM compared to group M. By using unpaired *t*-tests, *p*-value was < 0.0001. The total dose of diclofenac given was less in Group CM compared to Group M. Pulse rate and Mean arterial pressure were not significant. No significant difference with respect to hypotension and bradycardia (*p*-value > 0.05). *Conclusion:* The duration of postoperative analgesia seems to be augmented by the combination since these are more prolonged than what is expected with either of the drugs used alone as adjuvants.

Keywords: Spinal Anesthesia; Intrathecal Bupivacaine; Randomization; Visual analog scale; hypotension; postoperative analgesia.

How to cite this article:

Archana Amol Gautam, Vishnu Madhusoodanan. Magnesium Sulphate with and Without Clonidine as Adjuvant to Bupivacaine for Lower Abdominal Surgeries: A Randomised Clinical Trial. Indian J Anesth Analg. 2019;6(5 P-II):1731-1736.

Introduction

The task of medicine is to preserve, to restore health and to relieve pain. Understanding pain is essential to both these goals.[1] Pain is derived from the Latin word *poena* which means 'penalty or punishment'.[2] Postoperative pain relief is a growing concern for an anesthesiologist as an uneventful postoperative period makes surgery a comfortable proposition for surgical patients.[3] Perkins and co-workers provided an insight into the reality that poorly managed acute pain like postoperative pain can lead to the occurrence of chronic pain.[4] Spinal anesthesia, defined, as the regional anesthesia obtained by blocking the conduction of nerve impulses is a popular and common technique used worldwide. The advantages of an awake patient,

Corresponding Author: Vishnu Madhusoodanan, Resident, Department of Anesthesia, Krishna Institute of Medical Sciences, Malkapur, Karad (Dist. Satara), Maharashtra 415539, India.

E-mail: vishnu.or.m12@gmail.com

Received on 09.07.2019, **Accepted on** 16.08.2019

simple to perform, offers rapid on set of action, minimal drug cost, relatively less side effects and rapid patient turnover has made this the choice of many surgical procedures. Intrathecal clonidine is being extensively evaluated as an alternative to neuraxial opoids for control of pain and has proven to be a potent analgesic, free of at least some of the opoid related side effects.[5] It prolongs the necessary blockade and reduces the amount or concentration of local anesthetic required to produce postoperative analgesia.[6] Adding magnesium sulfate, on other hand, may improve the quality and increase the duration of spinal anesthesia.[7] Magnesium sulfate ($MgSO_4$), which is the fourth most plentiful cation in the body, proved to have antinociceptive effects in animal and human model of pain. This present study was designed to evaluate the efficacy and to know the duration of intraoperative and postoperative analgesia when clonidine with $MgSO_4$ was added as an adjunct to bupivacaine in comparison with $MgSO_4$ alone added as an adjunct to bupivacaine.

Materials and Methods

Study Design: Prospective, Randomized double blind, controlled trial

Study Settings: Krishna institute of medical sciences and hospital, Karad

Study Duration: 2 years between 2012 and 2014

Study Population: Those patients posted for elective lower abdominal and lower limb surgeries.

Sampling Technique: Purposive sampling technique

Inclusion criteria:

1. ASA physical status I and II
2. Valid informed consent

Exclusion criteria:

1. ASA III and IV
2. Contraindication to regional anesthesia.
3. Significant coexisting systemic disorders like neuromuscular diseases, neuronal degenerative disorders, bleeding and hematological disorders, cardiac disorders or gestational diabetes.
4. History of allergy to bupivacaine or clonidine.
5. History of opioid, clonidine medication or magnesium treatment prior to surgery
6. Parturients
7. Patient refusal
8. History of seizures

Sample Size: Sample size was calculated based on onset of sensory block to detect that onset will be earlier by 3.1 min (SD ± 0.6) and duration of analgesia will be prolonged by at least 50 min (SD ± 35) more, with α value of 0.05, power >95%

Ethical Consideration: The study was approved by Institutional ethics committee.

Consent type: Written informed consent.

Methodology:

Seventy adult patients of each gender, randomly divided into two groups of 35 each were included in the study:

Group M (n=35) received 3 ml of 0.5% hyperbaric bupivacaine, preservative free magnesium sulphate 50%, 0.1 ml (50 mg) and preservative free normal saline 0.5 ml.

Group CM (n=35) received 3 ml of 0.5% hyperbaric bupivacaine, preservative free magnesium sulfate 50%, 0.1 ml (50 mg) and clonidine 0.5 ml (75 μg).

The procedure of double blinding was done by 2 separate anesthetist and patient underwent thorough preoperative evaluation which includes history taking, general physical examination and investigation.

Patient was shifted to the operation table; intravenous access was obtained on the forearm with 20 Gauge intravenous cannula and Lactated Ringer's solution 500 mL was infused intravenously before the block. The monitors connected to the patient included noninvasive blood pressure, oxygen saturation using pulse oximeter and electrocardiogram. Baseline PR and MAP was recorded.

A lumbar subarachnoid block was performed under strict aseptic precautions with the patients in the left lateral position with a 25-gauge Quincke needle at L 2-3 or L 3-4 using a midline approach. After free flow of cerebrospinal fluid (CSF), the

premixed solution was injected over 10 sec with the needle orifice directed cephalad, making sure of negative aspiration for blood. Patients were made to lie supine immediately after the completion of injection. The time of injection of the drug was recorded as 0 minute. Vital parameters such as PR and MAP were monitored at baseline, after drug injection and every 5 min for first 20 min and 15 min thereafter till end of the surgery were studied and duration of effective analgesia was also studied. Duration of analgesia was defined as the time from the intrathecal injection to VAS > 4. VAS was also recorded 3, 6, 12 and 24 hours postoperatively. Intramuscular injection Diclofenac 75 mg was given for rescue analgesia whenever the pain score was > 4.

Statistical Analysis: Patients were allocated to the two insertion techniques randomly by computer generated random numbers. Parametric data were expressed as mean and standard deviation (S.D) and analyzed using the independent t test using SPSS (version 22.0). $p < 0.05$ is considered statistically significant.

Results

As per Table 1 most of the patients belonged to the age group between 41 and 50 years in both the groups. By using independent sample t-test, *p*-value was 0.10. Since the *p*-value is > 0.05 therefore there is no significant difference between age (years) in

Table 1: Agewise Distribution of Patients in Both the Groups

Age (Year)	Group M		Group CM	
	No. of Patients	Percentege (%)	No. of Patients	Percentege (%)
≤20	00	00	03	8.57
21–30	02	5.71	06	17.14
31–40	09	25.71	08	22.86
41–50	11	31.43	08	22.86
51–60	07	20	05	14.28
61–70	05	14.29	05	14.28
>70	01	2.86	00	00
Total	35	100	35	100
Mean age ± SD	48.28 ± 12.9		42.6 ± 15.5	
p-Value	0.101			

Table 2: Comparison of Distribution of Patients in Group M and Group CM with Respect to the Type of Surgeries

Type of Surgery	Group M		Group CM	
	No. of Patients	Parcentege (%)	No. of Patients	Percentege (%)
Vaginal Hysterectomy (VH)	5	14.3	5	14.3
Abdominal Hysterectomy (AH)	5	14.3	6	17.2
Heranioplasty	6	17.2	5	14.3
Open appendicectomy (OA)	3	8.6	3	8.6
Exploratory Laparotory (Exp lap)	2	5.7	2	5.7
Jaboulay's Procedure	2	5.7	2	5.7
CRIF with tibia nailing (TN)	2	5.7	3	8.6
ORIF with tibia plating (TP)	3	8.5	3	8.6
Debridement	3	8.5	1	2.8
STSG	4	11.5	5	14.3
Total	35	100	35	100

Table 3: Comparison of Duration of Analgesia (Minutes) in Group M and Group CM

Time in Minutes	Group M	Group CM
Minimum	160	360
Maximum	260	480
Mean ± SD	218.42 ± 23.88	430.85 ± 32.39
p-value	<0.0001	

both the groups. While distribution of gender was almost equal in both.

As per Table 2 distribution of patients according to the type of surgeries in Group M and Group CM. Both the groups are comparable with respect to the type of surgery.

As per Table 3 the duration (minutes) of analgesia was prolonged in Group CM compared to Group M. By using unpaired *t*-tests, *p*-value was <0.0001. Since the *p*-value is <0.05, hence the difference between duration (minutes) of analgesia in Groups M and CM is statistically significant. 95% confidence interval of the difference: 198.86 to 226.00.

According to Figure 1 shows comparison of mean pulse rate in Group M and Group CM Statistical evaluation done between the two groups showed no significant difference in mean pulse rate at any interval, (*p*-value = 0.676).

Figure 2 shows comparison of mean arterial pressure in Group M and Group CM. Statistical evaluation done between the two groups did not show a significant difference in mean arterial pressure at any interval, (*p*-value = 0.25).

As per Table 4 shows comparison of total dose of diclofenac given in the postoperative period in Group M and Group CM. The total dose of diclofenac given was less in Group CM compared to Group M. By using unpaired *t*-tests, *p*-value was <0.0001. Since the *p*-value is <0.05, hence there is a statistically significant difference between total

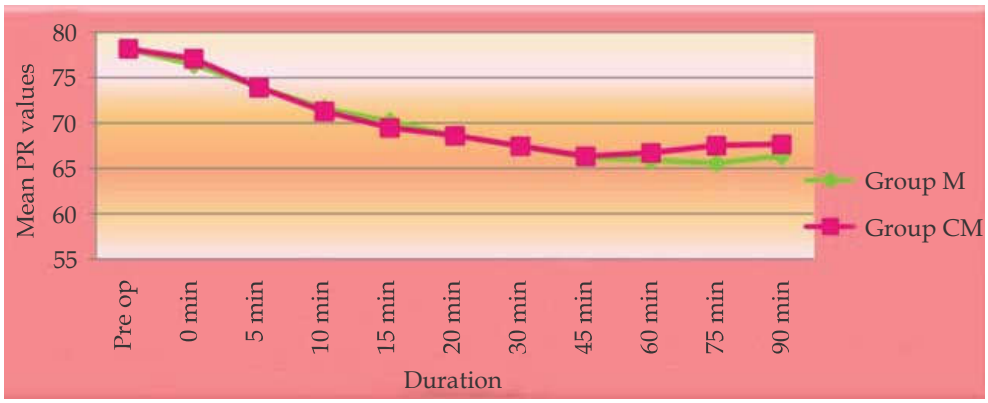

Fig. 1: Mean pulse rate in both the groups at different time intervals.

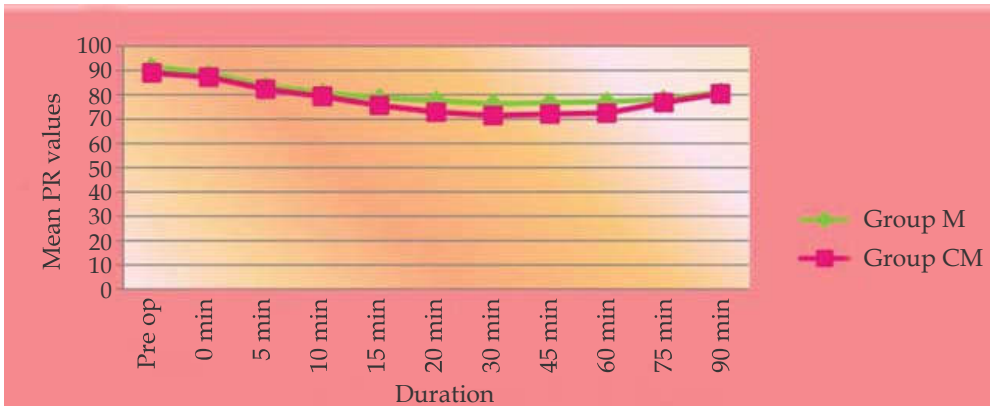

Fig. 2: Mean arterial pressure in both the groups at different time intervals.

Table 4: Comparison of Total Dose of Diclofenac (mg) Given in the Postoperative Period in Group M and Group CM

Total dose (mg)	Group M	Group CM
Minimum	150	75
Maximum	300	150
Mean ± SD	216.42 ± 43.70	98.57 ± 35.32
p-value	<0.0001	

Table 5: Comparison of Distribution of Patients in Group M and Group CM with Respect to their Adverse Effects

Adverse Effect	Group M		Group CM		*p*-value
	No. of Patients	Percentage (%)	No. of Patients	Parcentege (%)	
Hypotension	02	5.7	05	14.2	0.428
Bradycardia	02	5.7	03	8.5	1.000
PONV	00	00	00	00	
Sedation	09	25.7	22	62.8	0.003
Urinary Retention	00	00	00	00	
Pruritis	00	00	00	00	

dose of diclofenac given in the postoperative period in Groups M and CM. 95% confidence interval of the difference: –136.81 to –98.904.

As per Table 5 Statistical evaluation done by using Fischer's exact test between the two groups showed no significant difference with respect to hypotension and bradycardia (p-value > 0.05) but showed a statistical significant difference with respect to sedation (p-value < 0.05).

Discussion

The gate control theory of pain has had considerable influence on the anesthesiologists management of pain focusing attention on the unique pharmacology of the dorsal horn of the spinal cord. The technique has implications in acute and chronic pain therapy. A typically modern view of perioperative pain is to view it as an impediment to recovery. Aggressive methods are often used to minimize pain to facilitate hospital discharge and a rapid return to normal functional activity.[8] Our study design consisted of 70 patients, ASA physical status I, II undergoing elective lower abdominal and lower limb surgeries under spinal anesthesia were randomly divided into two groups after taking informed consent. In a study conducted by Stephen Strebel, *et al*.[9] intrathecal clonidine in dose of 37.5 µg, 75 µg and 150 µg used showed no intergroup differences in mean arterial BP decrease ≥30% (21% ± 13%, 25% ± 14%, 26% ± 12%, and 25% ± 13%) and also showed duration of analgesia was prolonged with higher doses (295 ± 80 min, 343 ± 75 min, 381 ± 117 min, and 445 ± 136 min). In our study, the time for first rescue analgesic required was prolonged ingroup CM with 430.85 ± 32.39 min and in Group M it was 218.42 ± 23.88 min which was statistically significant (p < 0.0001). Stephen S, *et al*.[9] conducted a study to evaluate dose response relationship of intrathecal clonidine at small doses (<150 µg) with respect to prolonging bupivacaine spinal anesthesia in 80 orthopedic patients. The duration of analgesia was prolonged in group receiving bupivacaine andclonidine (381 ± 117 min vs 295 ± 80 min) compared to group receiving bupivacaine alone. Shashni, *et al*.[10] in her study conducted on 124 patients showed duration of analgesia was prolonged in group receiving bupivacaine and magnesium (206.452 ± 26.246 min vs 185.323 ± 12.89 min) compared to group receiving bupivacaine and midazolam. Our study results show that the duration of analgesia is prolonged by combination of clonidine and magnesium sulfate with bupivacaine than magnesium sulfate alone or what is known to occur with clonidine alone. Clonidine augments the action of magnesium sulfate when given as a combination compared to what is documented with either drug. Also in a study conducted by I. Dobrydnjov *et al*.[11] on 45 patients showed the duration of analgesia in clonidine group (30 µg) (253 ± 71 min vs 171 ± 65 min) in control group. Duration of analgesia was higher in our study which is as expected considering the different doses of clonidine and bupivacaine used. This suggests that the prolongation of duration of analgesia is dose dependant. In our study the total dose of diclofenac given in the postoperative period was higher in Group M 216.42 ± 43.70 mg when compared to Group CM 98.57 ± 35.32 mg which was statistically significant (p < 0.0001). In our study also there was significant reduction in the VAS scores of the patients receiving clonidine in comparison with higher VAS scores in control group patients in the first twenty-four hours postoperatively. The requirement of diclofenac in the first 12 hours postoperatively was reduced in clonidine group compared to the control group. These results are comparable with the results in a study conducted by Gurudutta CL *et al*.[12] on 50 patients showing the 6-hour postoperative requirement of diclofenac injection was less in group receiving clonidine and bupivacaine. Also Sethi *et al*.[13] in his study showed that the number of injections of diclofenac required in 24 hours was also significantly higher for bupivacaine group (mean – 2.66) than the clonidine and bupivacaine group (mean – 1.16) [p < 0.05]. Our study results

concur with these studies and imply better quality and prolongation of analgesia postoperatively, and reduced need of analgesics with the use of intrathecal clonidine in our study, hypotension was 14% and bradycardia 9% in Group CM compared to 6% hypotension and 6% bradycardia in Group M which was statistically insignificant. Also, in our study 64% of patients in Group CM had sedation compared to 26% of the patients in Group M which was statistically significant ($p < 0.05$). Our study results are comparable with a study conducted by Dobrydnjov *et al.*[11] showing there is no incidence of hypotension and bradycardia with small dose of clonidine. Kothari *et al.*[14] in his study showed incidence of sedation in clonidine with bupivacaine group was 64.28% which was statistically significant ($p < 0.05$).

Conclusion

Based on the present study combination of clonidine (75 µg) and magnesium sulfate (50 mg) as adjuvants with hyperbaric bupivacaine 0.5% (15 mg) for subarachnoid blockade results in earlier onset of action and extended postoperative analgesia. The duration of postoperative analgesia seems to be augmented by the combination since these are more prolonged than what is expected with either of the drugs used alone as adjuvants. This approach to pain therapy may hold promise, that favourable outcomes such as successful analgesia may be achieved.

Source of Funding: None

Conflict of Interest: None

References

1. Howard LF, Joseph BM. Pain-Pathophysiology and Management. In Harrison's Principles of Internal Medicine, 15th Edition, McGrawHill, 2001.
2. Ronald DM (editor). Miller's anesthesia. 7th ed. Churchill Livingstone 2009.pp.3-54. 2767; 2758, 2760-7, 782-807, 1544, 1343, 2228.
3. Vaswani RK, Raiger LK, Purohit R, *et al.* The effect of intrathecal midazolam on postoperative pain relief in orthopaedic surgery. Hospital Today 2002;7(4):150–53.
4. Perkins FM, Kehlet H. Chronic pain as an outcome of surgery. A review of predictive factors. Anesthesiology. 2000;93:1123–33.
5. Eisenach JC. Overview: First international symposium on α-2 adrenergic mechanisms of spinal anesthesia. Reg Anaesth. 1993;18(4S):1–4.
6. Dobrydnjov I, Samarutel J. Enhancement of intrathecal lidocaine by addition of local and systemic clonidine. Acta Anesthesiol Scand. 1999; 43:556–62.
7. Niemi L. Effects of intrathecal clonidine on duration of bupivacaine spinal anesthesia, hemodynamics and postoperative analgesia in patients undergoing knee arthroscopy. Acta Anesthesiol Scand. 1994;38:724–8.
8. Larson MD. History of anesthetic practice, Chapter 1 in Miller's Anesthesia, Sixth Edition, Elsevier Churchill Livingstone. 2004:3–54.
9. Strebel S, Gurzeler JA, Schneider MC, *et al.* Small-Dose Intrathecal Clonidine and Isobaric Bupivacaine for Orthopedic Surgery.Anaesth Analg. 2004;99:1231–8.
10. Shashni S, Nair AS, Gopal T. Clinical effects of intrathecal midazolam versus intrathecal magnesium sulfate as adjunct to hyperbaric bupivacaine: a comparative study. Indian j pain. 2013;27:175–81.
11. Dobrydnjov I, Axelsson K, Thorn SE, *et al.* Clonidine Combined with Small-Dose Bupivacaine During Spinal Anesthesia for Inguinal Herniorrhaphy; A Randomized Double-Blinded Study. Anaesth Analg. 2003;96:1496–503.
12. Gurudutta CL, Svenkatesh G *et al.* A Prospective randomized controlled study of the effect of intrathecal clonidine with hyperbaric bupivacaine 0.5% for lower abdominal surgeries. Karnataka Anesthesia J. 2008;9(2).
13. Sethi BS, Samuel M, Sreevastava D. Efficacy of Analgesic Effects of Low Dose Intrathecal Clonidine as Adjuvant to Bupivacaine. Indian Journal ofAnesthesia. 2007;51(5):415-19.
14. Kothari N, Bogra J, Chaudhary AK. Evaluation of analgesic effects of intrathecal clonidine along with bupivacaine in cesarean section. Saudi J Anaesth. 2011;5(1):31–35.