Original Research Article

Indian Journal of Anesthesia and Analgesia
2018; 5 (2): 173-180
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.5218.4

A Comparative Study to Evaluate Efficacy of Two Doses of Intrathecal Clonidine (15mcg Versus 30mcg) as an Adjuvant to Bupivacaine for Prolongation of Spinal Anaesthesia

Anil Kumar Jain[1], Madhavi Santpur[2], Jai Ram Thakur[3], Karishma Bansal[4], Swati Kanchan[5]

[1]Assistant Professor [2]Associate Professor [3]Professor [4,5]PG Student, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Haryana 133207, India.

Abstract

Background: Clonidine, an α2-agonist, has been used intrathecally as an adjuvant to bupivacaine in spinal anaesthesia, for prolonging anaesthesia and postoperative analgesia. This study was designed to compare efficacy of two doses of intrathecal clonidine (15μg versus 30μg) for prolongation of anaesthesia, with maintainance of heamodynamic parameters, to find out lowest possible effective dose. *Methods:* Sixty patients, scheduled to undergo lower abdominal surgery, were enrolled. They were randomly divided into two groups, of 30patients in each group. Group BC_{15} received 15mg (3ml) of hyperbaric bupivacaine plus 15μg clonidine plus 0.1ml of normal saline and Group BC_{30} received 15 mg hyperbaric bupivacaine plus 30 μg (0.2ml) clonidine, thus keeping volume of injectable solution constant to 3.2 ml, in both groups. *Results:* Highest level of sensory block achieved, was recorded which was almost similar in both groups. Time taken to achieve highest level of sensory block , time to achieve two segment regression, time to achieve regression to L_1 dermatome , time to first analgesic request , time to achieve maximum Bromage scale 4, time to achieve regression back to minimum Bromage scale 1 and haemodynamic changes, showed no stastically significant difference amongst both groups (P value >0.05). *Conclusion:* Both doses of intrathecal clonidine i.e.15μg and 30μg with bupivacaine, produce equal prolongation of sensory and motor block alongwith time to first analgesic request.So, clonidine15μg intrathecally with bupivacaine is preferred over 30μg or higher dose to achieve prolongation of desired sensory and motor block alongwith postoperative analgesia with clinically insignificant haemodynamic effects.

Keywords: Intrathecal; Clonidine; Adjuvant; Postoperative Pain; Haemodynamics.

Introduction

Spinal anaesthesia is immensely popular for lower abdominal and lower extremity surgeries. However, it has some limitations. For example, it has fixed duration of action, which, sometimes falls short of and general anaesthesia has to be supplemented.

To overcome this and for post-operative analgesia, some adjuvants have been tried intrathecally along with local anaesthetics like bupivacaine, to prolong their effect e.g. midazolam [1], α-2 agonists like clonidine [2], neostigmine [3,4], fentanyl [5], ketamine. But some side effects of these adjuvants were reported e.g. opiods cause nausea, vomiting and respiratory depression. Parenteral alpha-2 agonists have also been tried for the same purpose, but since they have to be given in higher doses, they cause significant side effects in the form of hypotension and bradycardia, because of systemic actions.

So intrathecal (IT) alpha-2 agonists have been studied by different researchers in varying doses, with variable efficacy and side effects.

Thus, aim of this comparative study, was to evaluate efficacy of two doses of IT clonidine (15μg versus 30 μg) in prolongation of spinal anaesthesia with maintainance of haemodynamic parameter.

Corresponding Author: Madhavi Santpur, Associate Professor, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Haryana 133207, India.
E-mail: aniljain.bbmb@gmail.com

Received on 13.11.2017, **Accepted on** 23.01.2018

Material and Methods

Patients

After approval by institutional ethical committee, the study was conducted at Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana Distt Ambala (Haryana). A total of 60 patients undergoing elective lower abdomen surgeries, under spinal anaesthesia were enrolled for the study. It was designed in the form of a prospective, randomized and double blinded study. All patients were allocated randomly by a computer generated number, in two groups, of 30 patients in each group. GROUP BC_{15} received 15 mg (3 ml) of 0.5% hyperbaric bupivacaine plus 15 µg (0.1 ml) of clonidine,with addition of 0.1 ml of normal saline to make total 3.2 ml solution and Group BC_{30} received 15 mg (3 ml) of 0.5% of hyperbaric bupivacaine plus 30µg (0.2 ml) of clonidine. So, in both groups, the volume of solution to be injected intrathecally was kept constant i.e. 3.2 ml.

Inclusion Criteria

All patients between 18 to 60 years of age ,of either gender with ASA grade I and II, undergoing elective surgical procedures in lower abdomen , under spinal anaesthesia were considered for study. Written informed consent was obtained in all cases for inclusion in study population and undergoing surgery.

Exclusion Criteria

1. History of hypersensitivity to bupivacaine or clonidine,
2. History of taking β-blockers, α2-agonists including methyldopa,
3. Patients who will not give consent for spinal anaesthesia,
4. All contraindications to spinal anaesthesia e.g. sepsis of back, spine deformity, coagulation disorders etc and
5. Any cardiovascular disease like ischaemic heart disease, congenital heart disease, arrhythmias, bradycardia etc.

Study Procedure

All patients were given alprazolam 0.25 mg and ranitidine 150 mg orally on night prior to surgery. A fasting period of eight hours was ensured. In operation theatre, a multipara monitor was applied to patient to record electro cardiogram (ECG), oxygen saturation (SpO_2) and non- invasive blood pressure (NIBP). Intravenous line was secured with 18G cannula. Preloading was done with 12 ml/kg of ringer lactate 15-20 minutes before start of subarachnoid block. Basal blood pressure, pulse and SpO2 was recorded. Under all aseptic conditions, lumbar puncture was done in lateral decubitus position at L_{3-4} position and drug injected as per group, mentioned above. Sensory block was judged by pin prick method using short bevelled 25G needle. It was checked at regular interval of two minutes to see highest level of block. Time taken to achieve highest level was recorded. Recovery from sensory blockade was recorded for two segment regression. Further, it was recorded upto L_1 dermatomal level and duration of sensory block was considered as time from intrathecal injection to regression till L_1. Similarly, duration if motor block was considered as the time from intrathecal (IT) injection of drug to the time till regeression to Bromage scale 1. Total duration of analgesia was assessed by the timing of first rescue analgesic administered. During and after surgery, time to rescue analgesia was recorded and treated with injection diclofenac sodium 75mg intravenously, whenever VAS was >4.

Motor block was assessed at the same time intervals as for sensory block, with modified Bromage scale as under:

1. Grade1. Free movement of legs and feet.
2. Grade 2. Just able to flex knees with free movement of feet.
3. Grade 3. Unable to flex knees with free movement of feet.
4. Grade 4. Unable to move legs or feet.

Time to have maximum degree of block as per above scale and its regression to Bromage scale 1 was recorded. Haemodynamic parameters were recorded, after subarachnoid block: (a) Every 2 minutes up to 10 minutes (b) Every 5 minutes upto 30 minutes (c) Every 15 minutes upto 2 hours and (d) every 30 minutes for 5 hours after subarachnoid block.

The level of sedation was observed intraoperatively. Any episode of hypotension (i.e. 20% or more reduction of blood pressure from baseline) was recorded and treated with increments of intravenous mephenteramine 6mg and intravenous fluids. And any episode of bradycardia (i.e. heart rate of 50/minute or below this) was also recorded and treated with injection atropine in required dose.

The results were evaluated, compiled and appropriate statistical analysis was done, using unpaired Student T-test.

Outcome

The primary outcome was to compare efficacy of two doses of intrathecal clonidine (15µg versus 30µg) as an adjuvant to bupivacaine for prolonging sensory and motor block of spinal anaesthesia and post-operative analgesia. Secondary outcome was to compare side effects like hypotension, bradycardia, sedation , nausea and vomiting etc.

Results

Observations of all 60 patients enrolled in the study were included for analysis. Their age, sex, weight, height and ASA status were comparable amongst both groups (Table 1). All patient underwent Gynaecology and Obstetrical surgery. Highest level of sensory block achieved, was recorded which was almost similar in both groups. Time taken to achieve highest level of sensory block, time to achieve two segment regression, time to achieve regression to L_1 dermatome, time to first analgesic request, time to achieve maximum

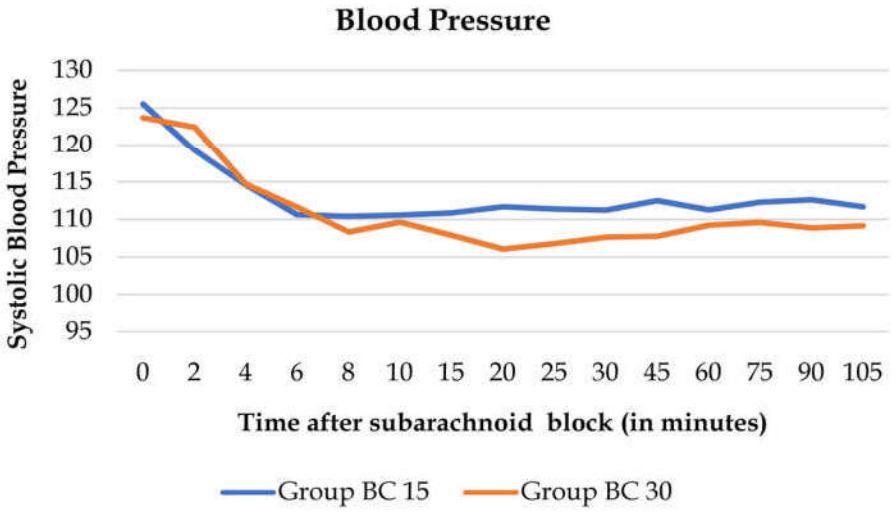

Fig. 1: Comparison of Systolic Blood Pressure of mean±standard deviation between groups BC_{15}& BC_{30}, at different time intervals after subarachnoid block

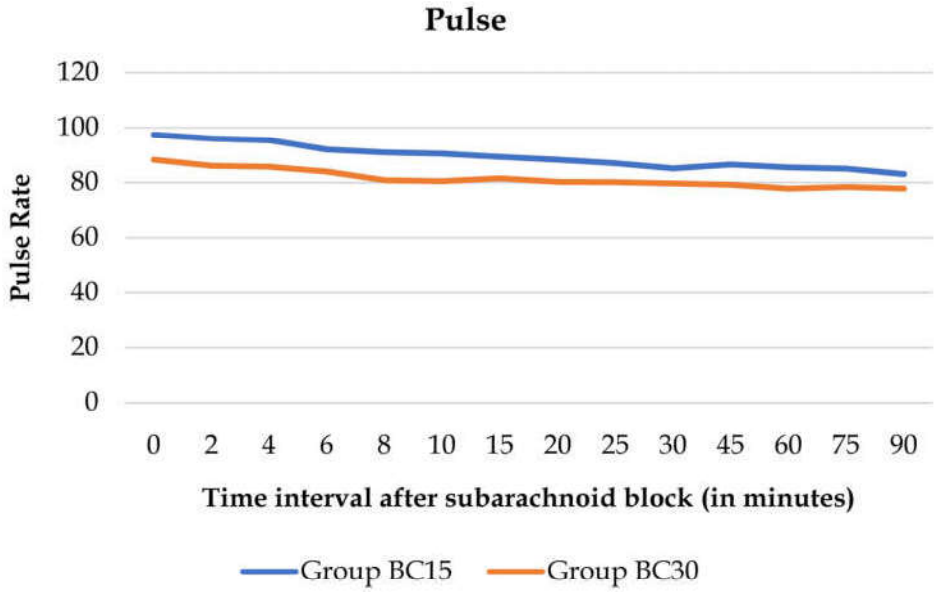

Fig. 2: Comparison of Pulse Rate of mean±standard deviation between groups BC_{15}& BC_{30}, at different time intervals after subarachnoid block

Table 1: Patient characteristics

Age (years)	35.33 ± 11.80	41.33 ± 11.95
Weight (kgs)	61.47 ± 8.32	61.33 ± 12.37
Height (cms)	151.33 ± 4.79	152 ± 4.78
ASA I:II	22:8	23:7

Table 2: Comparison of characteristics of Analgesia, Sensory Block and Motor Block (P-value <0.05 was considered statistically significant)

	Group BC_{15}	**Group BC_{30}**	**p-value**
Highest level of sensory block:			
T_4	14 patients	16 patients	
T_6	14 patients	12 patients	
T_8	2 patients	2 patients	
Time (in minutes) to achieve highest level of sensory block	6.033 ± 1.35	5.73 ± 1.48	0.23
Time (in minutes) to achieve two segment regression	154.2 ± 14.54	157 ± 14.12	0.26
Time (in minutes) to achieve regression to L_1 dermatome	209.93 ± 16.26	217.13 ± 15.57	0.09
Time (in minutes) for first analgesic request	234.3 ± 18.43	243.9 ± 20.19	0.06
Time (in minutes) to achieve highest Bromage Scale 4	6.033 ± 1.35	5.73 ± 1.484	0.23
Time (in minutes) to achieve regression back to lowest Bromage Scale1	246.2 ± 18.56	252.87 ± 15.45	0.08

Table 3: Incidence of side effects

	Group BC_{15}	**Group BC_{30}**
Bradycardia	2 (7%)	2 (7%)
Hypotension	6 (20%)	9 (30%)
Sedation	0	4 (13%)
Nausea	0	1 (3%)
Vomiting	0	1 (3%)

Bromage scale 4 and time to achieve regression back to minimum Bromage scale 1, were recorded and analysed (Table 2). These parameters showed no statistically significant difference amongst both groups (P value >0.05) as shown in Table 2.

Mean systolic blood pressure (SBP) varied from baseline of 126±SD12 mmHg to minimum reading of 110±SD13 in group BC_{15} and from baseline of 124±SD14 mmHg to minimum reading of 106±SD8.9 mmHg in group BC_{30}, during surgery Comparison of difference of SBP±SD from baseline to SBP±SD after an hour of surgery (i.e. till the time, data of maximum number of patients is available, in both groups), amongst both groups is not statistically significant (P-value 0.34). As shown graphically (Figure 1), both groups show steady and almost equal trend of fall in blood pressure. Most frequently, fall in blood pressure occurred around 8-10 minutes after intrathecal injection, in both groups and in some patients, episode of fall in blood pressure occurred upto 30 minutes. Six patients in group BC_{15} and nine patients in group BC_{30} had single episode of hypotension which got treated with single dose of 6mg mephenteramine, given once only in every such case.

Mean pulse rate (PR) varied from baseline of 97±SD15 to minimum of 83±SD8.8 beats/minute in group BC_{15} and from 88±SD10 to 78±SD8.4 beats/minute, respectively in group BC_{30}. Comparison of difference of pulse rate±SD from baseline to pulse rate after an hour of surgery , amongst both groups is not statistically significant (P-value 0.82). Whereas, in Group BC_{15}, baseline pulse rate was 97±SD15 and after an hour, it was 86±SD9.6, in group $BC_{30,}$ at similar timings the values were 88±SD10 to 78±SD8.4 beats/minute respectively. As shown graphically, (Figure 2) both groups showed steady downward trend of pulse rate after injection of drug to end of surgery. Both groups showed equal incidence of bradycardia i.e. two cases in each group (Table 3). All such cases had single episode of bradycardia and required one injection of atropine (0.6mg)for correcting the same.

Incidence of sedation, nausea and vomiting was more in group BC_{30} and there was no case with these side effects in group BC_{15}(Table 3).

Discussion

Clonidine is a partially selective agonist for α2 adrenoreceptors. Being lipophilic, like opiods, its intrathecal (IT) administration with local anaesthetic like bupivacaine, can prolong analgesia, post

operative period [6]. It has been used intrathecally as a sole analgesic for pain relief after caesarean delivery , in doses of 150 to 450 μg [7,8]. Its analgesic effect occurs by activating post synaptic α2 receptors in substantia gelatinosa of spinal cord. The rationale behind ITadministration of clonidine is to provide high concentration near these α2 receptors and then by blocking conductance of C and A-delta fibres, by increasing potassium conductance, thereby inducing hyperpolarization and hence, intensifying conduction block of local anaesthetics. The mechanism of clonidine-induced potentiation of spinal anaesthesia is reported to be mediated by presynaptic (inhibition of transmitter release) and postsynaptic (enhancing hyperpolarization) effects. Race et al [9]and Bonnet F et al [10] demonstrated potentiation of intensity and duration of motor blockade with in IT clonidine combined with local anaesthetics.The explanation of this could be again induction motor neurone hyperpolarization in ventral horn of spinal cord by α2 –adrenoreceptor agonist, to facilitate the local anaesthetic action.

Our results regarding duration of sensory block, motor block and post operative analgesia showed that there was statistically no significant difference in these parameters, between groups BC_{15} and BC_{30}. Prolongation of duration of these sensory, motor blocks and post operative analgesia is similar to the study done by Anil Thakur et al [11]. These researchers also used similar dosage of IT clonidine. They observed duration of sensory block as 270±39.69 and 276±40.62 minutes, motor block as 223.2±46 and 230.4±55 minutes and time to first analgesic request as 223,17±37 and 214.6±46 minutes, for groups BC_{15} and BC_{30} respectively versus control group which showed sensory block as 178.8±33, motor block as154.2±35 and time to first analgesic request as 140.4±37 minutes. With the same dosage of clonidine intrathecally, H Saxena et al [12] observed motor block time as 206.75±20 and 220.47±47 minutes and time to first analgesic request as 164.5±24 and 264.75±44 minutes, for groups BC_{15} and BC_{30} respectively. Dobrydnjov et al [13] suggested, after their study, suggested that analgesia significantly increases by 15mcg of intrathecal clonidine but increasing dose to 30mcg, does not increase duration of analgesia further.

In contrast tour study, Shah Bhavini et al [14], who used similar doses of IT clonidine, showed significantly more duration oftime to first analgesic request and that too was different in two groups. They observed these durations as 387.1±97 and 436.65±149 minutes respectively for groups BC_{15} and $BC_{30.}$. But, in their study, time to achieve two segment regession was 127.85±13 and 137±11 minutes and duration of motor block was 186.5±15 and 186.2±11 minutes, which were similar in both groups but were less than in our study. Also, S Vardhan etal [15], who used 30mcg IT clonidine with local anaesthetic, observed time to two segment regression was very less (i.e. 62.2 minutes) than in our study.

Various studies with different higher doses than our study have been done, doses varying from 50 mcg to 300 mcg IT clonidine. The results had been variable, regarding sensory and motor parameters. For example, Ranju Singh et al [16], OlfaKaabachi et al [17] and S Strebel et al [18] used 75mcg of clonidine intrathecally .The studies done by these researchers independently drew different results. They showed duration of sensory block as 199.26±17, 136±56 and 325±69 minutes respectively, with time to first analgesic request as 760.50±284, 461±147 and 381±117 minutes and by B S Sethi et al [19] as 614 minutes. But with the same dose of clonidine, Dan Benhamou et al [20] and I.vanTuiji [21] et al observed time to first analgesic request as only 183±80 and 129 minutes respectively. Duration of motor block with 75 mcg IT clonidine,by these researchers, has been recorded as 230±33 min by Ranju Singh et al [16], 205 minutes by B S Sethi et al [19], 198±50 min by Ajay Wahi et al [22], 252±79 min by OlfaKaabachi et al [17] and 172±62 minutes by Dan Benhamou et al [20].

Despite beneficial effect of intrathecal clonidine in enhancing sensory block, motor block and post operative analgesia , it is presumed to be associated with side effects of clonidine on perioperative *haemodynamics* (hypotension and bradycardia), sedation etc. Normally, after spinal anaesthesia with only local anaesthetic, hypotension and bradycardia can occur because of sympathetic blockade, leading to vasodilation with subsequent decrease in venous return and thereby decreasing intrathoracic blood volume (approximately 300 ml). Consequently central venous pressure, cardiac output, blood pressure and heart rate are reduced,depending upon height of sympathetic blockade .Bradycardia , and even asystole can occur due to blockade of cardioaccelerator sympathetic fibres,if level of anaesthesia involves T1-4 level and also due to BezoldJarisch reflex. Various strategies have been proposed to prevent these cardiovascular side effects e.g. prophylactic use of vasopressors like mephenteramine and vagolytics like atropine, volume preload or coload with crystalloids or colloids [23,24]. Addition of intrathecal clonidine to local anaesthetic, affects haemodynamics in a

complex manner because of opposing action at multiple sites. Clonidine, an α-2 adrenergic agonists produces sympatholysis and reduces blood pressure by its effects at specific brainstem nuclei and on sympathetic preganglionic neurons in spinal cord. These sympatholytic effects are counteracted by direct vasoconstriction, resulting from α-2 adrenergic agonists on peripheral vasculture [18]. These rather complex action of intrathecally injected α-2 adrenergic receptor agonists on haemodynamic variable, are further dependent on segmental site of injection, patient position, type of surgery e.g. caesarean section which has its own haemodynamics etc. In our study, haemodynamic changes were not clinically significant, as one dose of mephenteramine (6mg) was needed for treating hypotension which occurred in few cases in either group. Similarly, only one dose of atropine (0.6mg) was required for treating bradycardia which occurred invery few cases and that too equally in each group. Further, these incidence of haemodynamic changes are routinely observed in patients where spinal anaesthesia is given, with only local anaesthetic without addition of clonidine.

Dan Benhamou et al [20], in their study, on caesarean delivery patients, using IT75µg clonidine with local anaesthetic, achieving level upto T4 in all patients, observed that maximum haemodynamic changes occurred during 0-30 minutes in form of hypotension and bradycardia. These changes settled at slightly lower level than baseline after 80-120 minutes. They, alongwith studies by Alahuhuta et al [25] and Pederson H et al [26] (using very small amount of IT clonidine i.e.25-75 µg with local anaesthetic), showed increased duration of pain free interval compared from only spinal local anaesthetics, and without causing any significant side effect. Their study is in consonance with our study regarding timing of hypotension and bradycardia which, in our study, occurred from 0-30 minutes irrespective of whether patient was undergoing caesarean section or any other gynaecological or obstetrical surgery, as per scrutiny of our master chart. Ranju Singh et al [16] also observed fall in SBP occurred most frequently at either 3-6 min after SA or 5-10 min after delivery. The fall in SBP 3-6 min after SA is most likely due to sympatholysis by IT bupivacaine and not due to to IT clonidine because haemodynamic changes of clonidine after IT or other systemic administration starts within 30 minutes and reaches maximum within 1-2 hours [27]. In consonance with our study, Arora et al [28] also had similar observations regarding haemodynamic changes.

In contrast to our study, Anil Thakur et al [11] observed fall in blood pressure at 15-240 min and Dobrydnjov et al at 45-120 min whereas Grandhe et al [29] observed fall from 45 min to 8 hours after IT injection.

But Anil Thakur et al [11] has shown incidence of hypotension and bradycardia ,very similar to our findings. They observed 5 and 7 cases of hypotension in group BC_{15} and BC_{30} respectively and 2 cases of bradycardia in each group. Srivishnu et al [15] showed incidence of hypotension 12% and bradycardia as 27% with 30µg IT clonidine. But they observed 52% patients of hypotension and 21% of bradycardia, in control group. H Saxena et al [12] recorded hypotension as 10% and 20% in group BC_{15} and BC_{30} and bradycardia as15% and 30% patients, respectively. Higher doses of IT clonidine (75µg) in some studies recorded hypotension 24-29% and bradycardia 21%(Ranju Singh et al [16] and Olfa Kaabachi et al [17]).

Incidence of other side effects of IT clonidine was, sedation in 13% patients and that too in only group BC_{30}, in our study. Only one patient had nausea and vomiting. This is much less than in study done by H Saxena et al [12], who showed sedation in 15% and 40% patients in group BC_{15} and BC_{30} respectively, without any patient of nausea / vomiting, in either group. Shah Bhavini et al [14] observed sedation in 25% and 5% patients in BC_{15} and BC_{30} groups respectively. Even higher IT clonidine doses (75µg) inferred variable incidence of sedation, from 2% [17] to 40% [20] and nausea in 21% [17] and 14% [20] respectively.

Conclusion

From our results and above discussion, it is concluded that both doses of IT clonidine i.e. 15µg and 30µg with bupivacaine, produce equal prolongation of sensory and motor block alongwith time to first analgesic request. This prolonged effect also equals some of studies which have been done with higher doses of IT clonidine. So, clonidine15µg intrathecally with bupivacaine is preferred over 30µg or higher dose to achieve prolongation of desired sensory and motor block alongwith postoperative analgesia with clinically insignificant haemodynamic effects.

Financial or Other Competing Interests

None

References

1. Barti N, Madan R, Mohanty PR, Kaul HL. Intrathecal midazolam added to bupivacaine improves the duration and quality of spinal anaesthesia. Acta Anaesthesiol Scand 2003;47:1101-5.
2. Kothari N, Bogra J, Chaudhry AK. Evaluation of analgesiceffects of intrathecal clonidine alongwith bupivacaine in cesarean section. Saudi J Anaesth. 2011;5(1):31-5.
3. Roelants F. The use of neuraxial adjuvant drugs (neostigmine, clonidine) in obstetrics. Curr Opin Anaesthesiol. 2006;19(3):233-7.
4. Ven de Velde M, Berends N et al. Effects of epidural clonidine and neostigmine following intrathecal labour analgesia: a randomized double blind placebo-controlled trial; Int J obs Anaesth 2009 july;18(3): 207-14.
5. Hunt CO, Dutta S, Hauch M. Perioperative analgesia with subarachnoid fentanyl-bupivacaine. Anaesthesiology: 1987;67.
6. Chiari A, Lorber C, Eisenach JC, Wildling E, Krenn C et al. Analgesic and haemodynamic effects ofintrathecal clonidine as sole analgesic agent during first stage of labour: a dose-response study. Anaesthesiology 1999;91:388-96.
7. Filos KS, Goudas LC, Patroni O, Polyzou V. Intrathecal clonidine as a sole analgesic for pain relief after cesarean section. Anaesthesiology 1992;77: 267-74.
8. Filos KS, Goudas LC, Patroni O, Polyzou V. Haemodynamic and analgesic profile after intrathecal clonidine in humans.A dose-response study; Anaesthesiology 1994;81:591-601.
9. Racle JP, Benkhadra A, Poy JY, Gleizal B. Prongation of isobaric bupivacaine spinal anaesthesia with epinephrine and clonidine for hip surgery in the elderly. Anesth Anal 1987;66:442-6.
10. Bonnet F, Bran-Buisson V, Saada M, Boico O, Rostaing S, Touboul C. Dose-related prolongation of hyperbaric tetracaine spinal anesthesia by clonidine in humans. Anaes Anal 1989;68:619-22.
11. Anil Thakur, Mamta Bhardwaj, Kiranpreet Kaur, Jagdish Dureja, Sarla Hooda, Susheela Taxak. Intrathecal clonidine as an adjuvant to hyperbaric bupivacaine in patients undergoing inguinal herniorraphy: A randomized double blind study. Journal of Anaesthesiology Clinical Pharmacology; 2013;29(1):66-70.
12. H Saxena, S Singh, S Ghildiyal. Low dose intrathecal clonidine with bupivacaine improves onset and duration of block with haemodynamic stability. The Internet Journal of Anaesthesiology 23(1).
13. Dobrydnjov I, Axelsson K, Thorn SE, Matthiesen P, Klockhoff H, Olmstrom B, et al. Clonidine combined with small dose bupivacaine during spinal anesthesia for inguinal herniorrhaphy: A randomized double blind study. Anaes Anal 2003;96:1496-503.
14. Shah BB, Joshi SS, Shidhaye RV, Lakhe JN. Comparison of different doses of clonidine as an adjuvant to intrathecal bupivacaine for spinal anaesthesia and postoperative analgesia in patients undergoing caesarean section. Anaesth Pain & Intensive Care 2012;16(3):266-272.
15. Srivishnu Vardhan Yallpragda, Nagendra Nath Vemui, Mastan Sahib Shaik. Effect of adding clonidine to intrathecal bupivacaine on quality of subarachnoid block: A prospective randomized double blind study.: Anaesth Essays 2016;10:451.
16. Ranju Singh, Deepti Gupta, Aruna Jain. Effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain after lower segment caesarean section: A randomized control trial. Soudi Journal of Anaesthesia: 2013;7(3):283-290.
17. Olfa Kaabachi, Amine zarghouni et al. Clonidine 1microgm/kg is safe and effective adjuvant to plain bupivacaine in spinal anaesthesia in adolescents. Anaesth Anal 2007;105:516-9.
18. Strebel S, Gurzeler GA, et al: Small dose intrathecal clonidine and isobaric bupivacaine for orthopaedic surgery; a dose –response study: Anaes Anal. 2004 Oct;99(4):1231-8.
19. B.S. Sethi, Mary Samuel, Deepak Sreevastava. Efficacy of analgesic effects of low dose intrathecal clonidine as adjuvant to bupivacaine. Indian J Anaesth 2007;51 (5):415-19.
20. Benhamou D, Thorin D, Brichant JF, Dailland P, Milan D, Shneider M. Intrathecal clonidine and fentanyl with hyperbaric bupivacaine improves analgesia during caesarean section. Anaes Anal 1998;87:609-13.
21. I. Van Tuijl, W.A. Van Klei, B.M. Van et al. The effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain and morphine requirements after caesarean section; a randomized controlled trial. British Journal of Anaesthesia 2006;97 (3);365-70.
22. Wahi A, Amanjot K, Kartik ,A et al. Journal of Clinical and Diagnostic Research. 2016 Apr;10(4):UC06-08.s
23. Arndt, Joachim O.; Bomer, Walter; Krauth, Joachim; More. Incidence and Time Course of Cardiovascular Side Effects During Spinal Anesthesia After Prophylactic Administration of Intravenous Fluids or Vasoconstrictors Anesthesia & Analgesia. 1998 Aug;87(2):347-354.
24. Carpenter RL, Caplan RA, Brown DL, Stephenson C, Wu R. Incidence and risk factors for side effects of spinal anaesthesia. Anaesthesiology. 1992;76:906-16
25. Alahuhta S, Kangas-Saarela T, Hollmen AI, Edstrom HH. Visceral pain during caesarean section under spinal and epidural anaesthesia with bupivacaine. Acta Anaesthesiology Scand 1990;34:95-8.

26. Pederson H, Santos AC, Stinberg ES, et al. Incidence of visceral pain during caesarean section: the effect of varying doses of spinal bupivacaine. Anaes Anal 1990;69:46-9.
27. Eisenach JC, De Kock M, Klimscha W. Alpha (2)-adrenergic agonists for regional anaesthesia. A clinical review of clonidine (1984-1995). Anaesthesiology 1996;85:655-74.
28. Arora MV, Khan MZ, Choubey MS, Rasheed MA, Sarkar A. Comparison of spinal block after intrathecal clonidine-bupivacaine, buprenorphine-bupivacaine and bupivacaine alone in lower limb surgeries. Anesth Essays Res 2016;10:455-61.
29. Grandhe RP, Wig J, Yaddanapudi LN. Evaluation of bupivacaine-clonidine combination for unilateral spinal anaesthesia in lower limb orthopaedic surgery. J Anaesth Clin Pharmacol 2008;24:155-8.