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EFFECT OF ADDITION OF CLONIDINE TO INTRATHECAL BUPIVACAINE IN SPINAL ANAESTHESIA FOR ORTHOPAEDIC SURGERIES

Anaesthesiology

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ABSTRACT

Introduction-: Spinal anaesthesia is one of the most common approaches for most of lower limb surgeries. Clonidine has been recently introduced in India in the parenteral form (Cloneon, Neon laboratories). Hence there is a need to study its effects when used along with hyperbaric Bupivacaine, through intrathecal route. Therefore, this study was designed to study the effect of clonidine at different doses as an adjuvant to hyperbaric Bupivacaine, given intrathecally in orthopaedic surgeries.

Aims and objectives-: To evaluate the efficacy of intrathecal Clonidine in low doses (25 µg and 50 µg) as adjuvants to 0.5% hyperbaric Bupivacaine 12.5 mg for spinal anaesthesia in orthopaedic surgeries.

Methodology-: Ninety patients planed to undergo orthopaedic surgeries were subjected to this study. They were randomly divided into three groups of thirty each. Group A: Bupivacaine heavy (0.5%) 2.5 ml + No Clonidine, Group B: Bupivacaine heavy (0.5%) 2.5 ml + 25µg Clonidine, **Group C:** Bupivacaine heavy (.5%) 2.5ml + 50µg Clonidine

Results and conclusion-: Intrathecal administration of preservative free clonidine 25 mcg and 50 mcg along with 0.5% Bupivacaine significantly prolongs the duration of sensory and motor blockade. Significant prolongation of post-operative analgesia occurs with 50 mcg clonidine. Patients with 50 mcg clonidine remains calm, comfortable, minimally sedated throughout procedure with easily arousable with minimum hemodynamic instability like hypotension and bradycardia which can be easily managed.

KEYWORDS

INTRODUCTION

Spinal anaesthesia has many advantages over general anaesthesia which makes it the anaesthesia of choice in the present surgical practice. Some clinical studies suggest that postoperative morbidity and possibly mortality may be reduced when a neuraxial blockade is used either alone or in combination with general anaesthesia in some settings.

Bupivacaine is four times more potent than lignocaine (Relative in vitro Conduction-Blocking Potency) [1] and has longer duration of action. Its disadvantages are slow onset of action (5-10 min.) and decreased motor block. Hyperbaric Bupivacaine 0.5% is extensively used in India for spinal anaesthesia.

Numerous adjuvants can be added to hyperbaric Bupivacaine to prolong the duration of spinal anaesthesia, decrease the local anesthetic's dose requirement and increase the duration of post-operative analgesia.

All subtypes of α, *β*, and DA receptors have been found in various regions of the brain and spinal cord[15]. Central neuraxis injection of *α*-2 agonists, such as clonidine, act to produce analgesia, sedation, and cardiovascular depression. The increased duration of epidural or intrathecal anaesthesia by the addition of nonselective *α* agonists to the local anesthetic may also produce additional analgesia through this mechanism.

Clonidine hydrochloride is an imidazoline derivative with α-2 adrenergic agonist (220:1 *α*-2 to *α*-1) activity. Direct effects on the spinal cord mediated by α-2 post-synaptic receptors within the dorsal horn. Other additional benefits noted from a clonidine premedication include (1) blunted reflex tachycardia for intubation, (2) reduction of vasomotor liability, (3) decreased plasma catecholamines, and (4) dramatic decreases in MAC for inhaled gases or injected drugs. Oral clonidine was used to prolong lidocaine spinal anaesthesia[1], tetracaine spinal anaesthesia[2] and Bupivacaine spinal anaesthesia[3]. Hypotension was more pronounced after oral than intrathecal clonidine. Addition of intrathecal clonidine to Bupivacaine prolongs analgesia and decreases opioids consumption postoperatively more than oral clonidine[3]. Clonidine has antihypertensive properties and the ability to potentiate the effects of local anesthetics[4]. Clonidine has been shown to result in the prolongation of the sensory blockade and the reduction in the amount or the concentration of local anesthetic required to produce post operative analgesia. Clonidine also has the ability to prolong the motor blockade produced by Bupivacaine. Large doses of intrathecal clonidine (as much as 450µg) without local anesthetics, provides sedation and intense and long lasting postoperative analgesia, but inadequate for surgical anaesthesia and for this reason, clonidine has been used as an adjuvant to local anesthetics rather than alone[6]. Optimal doses of clonidine as an adjuvant to local anesthetic in subarachnoid block producing prolonged post operative analgesia and minimal side effects would be a true alternative to opioids with their dangerous side effects and to other technical procedures aimed at prolonging spinal anaesthesia and analgesia, such as combined spinal epidural anaesthesia, epidural analgesia, which have adverse effects, risks or technical difficulties. US FDA approved preservative free Clonidine formulations for epidural and intrathecal uses in 1996.

AIMS:

1. To study analgesic efficacy of intrathecal clonidine in both intraoperative and postoperative period

OBJECTIVES:

To evaluate the efficacy of intrathecal Clonidine in low doses (25 µg and 50 µg) as adjuvants to 0.5% hyperbaric Bupivacaine 12.5 mg for spinal anaesthesia in orthopaedic surgeries with regards to,

1. Onset and duration of analgesia.
2. Onset and duration of motor blockade.
3. Total duration of spinal anaesthesia.
4. Hemodynamic variation in intra and postoperative period.
5. Post operative period: Analgesic requirements and postoperative complications such as nausea, vomiting, sedation, hypotension and bradycardia.

MATERIAL AND METHODS

The study was presented for approval by hospital ethical committee and informed consent from all the participants was obtained. It was designed in the form of a prospective, randomized and double blinded study. Ninety patients planed to undergo orthopaedic surgeries were subjected to this study. They were randomly divided into three groups of thirty each.

INCLUSION CRITERIA:

- Patients in ASA I and II grades

- Age group of 20 – 50 years
- Undergoing elective orthopedics' surgeries.

EXCLUSION CRITERIA:

- Patients refusal for spinal anaesthesia
- Local infection at injection site
- Neurogenic pain
- Neurological deficit
- Coagulopathy
- Patient known to be sensitive or allergic to clonidine or Bupivacaine
- Patient with history of cardiac or respiratory diseases.
- Patient on chronic clonidine treatment for hypertension.

All patients planned in the study were undergone through pre-anaesthetic assessment including detailed case history, clinical examination and all necessary investigations.

All patients were kept to nil by mouth after 22:00 hrs. Inside the operation theatre, base line pulse rate and blood pressure (Systolic & Diastolic) were obtained. A wide bore intravenous line (no.18 or 20) was established and the patients were connected to IV Fluids and monitors such as ECG, SpO2, noninvasive blood pressure recording devices. Preloading was done with 20 ml.kg^{-1} of Ringers lactate solution about 15 minute before the intended time of intrathecal drugs administration. Patients were positioned in the sitting position and after adequate aseptic precautions lumbar puncture was performed at L3/L4 or L2/L3 intervertebral space using midline approach with in 25/27 gauge Quincke spinal needle. After ensuring a free flow of CSF, drug was injected. Then, patient allowed turning supine and a pillow kept below head. According to the administered concentration of drug, patients were grouped as following:

For Group-A: - Only 2.5 ml of Bupivacaine hyperbaric (0.5%) was added with 0.5 ml normal saline.

For Group –B:-0.25 ml of diluted Clonidine (25 µg) was double diluted with normal saline & was added with 2.5 ml of Bupivacaine hyperbaric (0.5%).

For Group –C: - 2.5 ml of Bupivacaine hyperbaric (0.5%) was added with 0.5 ml of diluted Clonidine as described (50 µg).

Following observations were noted intra and post operatively:

1. ONSET OF SENSORY BLOCKADE :

The Level and onset time of sensory blockage will be assessed using a 25 gauge short bevel needle every minute and was recorded as analgesia to loss of sensation to pin prick at calf.

2. DEGREE OF MOTOR BLOCKAGE :

The degree of motor blockage of the lower limbs was recorded every minute, Motor blockage was determined according to the Bromage scale.

3. DEGREE OF SEDATION :

Sedation was assessed with a four-point verbal rating scale.

4. INTRAOPERATIVE HEMODYNAMICS :

The parameters such as pulse rate, SpO_2 , non-invasive blood pressure and ECG were monitored by using multipara monitor (including pulse oxymetry and automated NIBP devices) and were recorded at 05 minutes interval upto 6 hrs.

Blood losses, urine output, IV fluid input were also noted. Patients were observed for any discomfort, nausea, vomiting, shivering, pain, bradycardia/ tachycardia and any other side effect. The need for additional medications was recorded.

IV fluid was administered in the form of Ringer's lactate, in calculated doses depending on the weight of the patient and further adjusted as per blood loss during surgery. A fall of blood pressure to more than 30% of mean arterial blood pressure (MAP) was treated with rapid infusion of 500 ml of RL and 6 mg of injection mephentermine intravenously if no response found to fluid administration. Bradycardia (heart rate less than 60/minute) was treated with intravenous atropine sulphate 0.6mg.

5. POSTOPERATIVE ANALGESIA :

All patients were observed in the post anaesthesia recovery room and then in the ward. Intensity of pain was measured using a 10 point visual analogue scale at half hourly interval by the nursing staffs that are unaware of the group the patient belonged to. The pain free post operative interval was observed and was recorded and rescue analgesia was provided by intravenous infusion of 50-100 mg tramadol when VAS score will be 4 or more than that.

6. COMPLICATIONS :

Intra and postoperative complications were noted and were managed accordingly. The mean and standard deviations for the observed data were calculated and was compared with the control and within clonidine groups, using Students t-test. A "p" value <0.05 was taken as significant.

OBSERVATION AND RESULTS

A total of ninety patients were studied in three groups, with 30 patients in each group. All the groups were studied in respect of age, height, ASA status and types of surgeries.

Table-1: DEMOGRAPHIC DATA

PARAMETER	Group-A (n=30)	Group-B (n=30)	Group-C (n=30)
Age (Years) Mean± SD	36.67 ±9.27	33.83 ±8.96	36.87 ±8.03
Height (cm) Mean ±SD	166.10 ±5.47	162.97 ±7.26	164.03 ±6.84

Table-1 shows the mean age and height distribution of patients in the three groups. There is no significant difference in the age and height of patients among the three groups.

Table- 2: ONSET OF SENSORY BLOCKAGE

PARAMETER	Group- A (n=30) Mean ± SD	Group- B (n=30) Mean ± SD	Group- C (n=30) Mean ± SD
ONSET OF SENSORY BLOCKAGE (in min.)	7.73±1.23	6.1±1.06	5.3±0.88

The mean time of sensory block was significantly lower ($p<0.05$) in all the Clonidine groups in dose dependent manner compared to control (Group-A), lowest in Group-C (5.30±0.88 min.).The differences in groups are statistically significant ($p<0.05$).

Table- 4: ONSET OF MOTOR BLOCKAGE

PARAMETER	Group-A (n=30) Mean ±SD	Group-A (n=30) Mean ±SD	Group-A (n=30) Mean ±SD
ONSET OF MOTOR BLOCKAGE (In min.)	11.63± 1.94	09.77± 1.87	07.70± 1.12

The mean time of onset of motor block was found lowest in Group-C (7.70±1.12 min.).All clonidine groups had a significantly quicker onset ($p<0.05$), as compared to control Group-A. There was no spastically significant differences in the extent of block achieved in any group, but it was achieved significantly faster in a dose dependent manner in all clonidine groups (Group-B and Group-C) as shown by the mean time to achieve it.

Table-5: DURATION OF SENSORY ANALGESIA

PARAMETER	Group- A (n=30) Mean ± SD	Group- B (n=30) Mean ± SD	Group- C (n=30) Mean ± SD
Duration Of Sensory Analgesia (in min.)	197.03±17.34	200.13±15.70	367.27±36.60

The mean duration of sensory analgesia was 197.03±17.34 min. in control Group-A, 200.13±15.70 min. in Group-B and 367.27±36.60 min. in Group-C. The dose dependent prolongation of sensory analgesia in Group-C compared to Group-A and Group-B was significant ($p<0.05$).

Table-6: DURATION OF MOTOR BLOCKAGE

PARAMETER	Group- A (n=30) Mean ± SD	Group- B (n=30) Mean ± SD	Group- C (n=30) Mean ± SD
Duration Of Motor Blockage (in Min.)	165.67±18.55	176.7±12.91	227.87±22.49

The mean duration of motor blockage is 165.66±18.55 min. in control

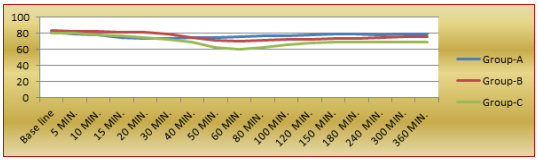
group-A, 176.70±12.91 min. in Group-B and 227.87±22.49 min. in Group-C. The prolongation of motor blockage in Group-C compared to other groups was significant ($p<0.05$).

Table-7: SEDATION SCORE

PARAMETER	Group- A (n=30) Mean ± SD	Group- B (n=30) Mean ± SD	Group- C (n=30) Mean ± SD
Sedation Score	0.03±0.18	0.20±0.48	1.07±0.74

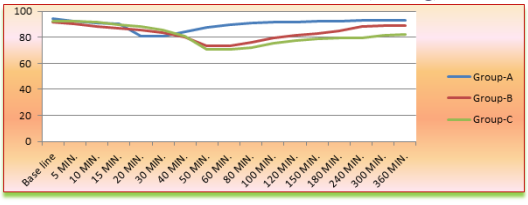
Patients in Group-C were more sedated than other groups ($p<0.05$). There is no stastically significant difference between group-A and group-B ($p>0.05$). There was no respiratory depression or desaturation in any patient in any group.

Figure-17: PULSE RATE (BEATS PER MINUTES)



This graph shows the variation in pulse rate in all groups at different time intervals upto six hours following intrathecal injection of drugs. Pulse rate decreased more in Group-C compared to other groups.

Figure-18: MEAN ARTERIAL PRESSURE (mmHg)



This graph shows the changes in mean arterial pressure (mmHg) in all three groups at different time interval following intrathecal injection of drugs. Blood pressure fall was more in Group-C when compared to other groups.

DISCUSION

Pain is the most frequent cause of suffering and disability, which seriously impairs the quality of life of millions of people worldwide. Clonidine is a selective partial agonist for α-2 adrenoreceptors. It is known to increase both sensory and motor block of local anesthetics. The analgesic effect following its intrathecal administration is mediated spinally through activation of post synaptic α-2 receptors in substantia gelatinosa of spinal cord. Clonidine for intrathecal use along with hyperbaric Bupivacaine 0.5% , which is most commonly used local anesthetic for spinal anaesthesia in our hospital, was chosen for the present study, since it represents a novel approach in providing postoperative analgesia in continuation with surgical anaesthesia. We observed that addition of clonidine improved the onset time, speed of spread and duration of block in a dose dependant manner.

Sensory blockade

Onset of sensory blockade : In our study the mean time for onset of sensory block is 7.73±1.23 min in control group and 6.10±1.06 min in clonidine Group-B (25µg) and 5.30±0.88 min in clonidine Group-C (50 µg). There is a statistically highly significant decrease in the onset of sensory blockade in clonidine group.

In a study conducted by **Grandhe PR et al**[15], authors observed onset of analgesia to be 7.6±2.2 mins in control group (7.5mg of hyperbaric Bupivacaine) and it was 7.1±4.2 mins and 8.2±3.4 mins in clonidine group (clonidine 1 µg/kg and 1.5 µg/kg respectively) which is more than the value in our study. This could be due to the less mass of hyperbaric Bupivacaine (7.5mg) used and patients were kept in the lateral position for 15 min after the administration of the drug and authors have not mentioned whether they have noted the onset of analgesia on the dependant side or on the non dependant side.

Maximum level of sensory blockade achieved: In our study the maximum level of sensory blockade achieved is T10 in the control group and is T6 in the clonidine Group-C (50 µg) and variable from T6 to T10 in Group-B (25 µg). This compares with the study conducted by **Dobrydnjov I et al**[10] where in by adding clonidine 15 µg to 6 mg of 0.5% hyperbaric Bupivacaine the maximum level of blockade achieved was 4 segment higher compared to control group.

The highest level block was similar in all three groups in the present study, as also reported by **Grandhe et al**[14] and **B.S.Sethi et al** [7] while **Dobrydnjov et al**[10] had found a difference of 2 to 4 segments with 30 µg clonidine on the operated side using a unilateral block.

Duration of analgesia: The mean duration of sensory analgesia was 197.03±17.34 min. in control Group-A, 200.13±15.70 min. in Group-B and 367.27±36.60 min. in Group-C. This is statistically highly significant. Our study concurs with the study conducted by **Strebel S et al**[8] who observed the mean duration of analgesia to be 381±117 mins when using clonidine of 75 µg and **Grandhe PR et al**[14] observed the mean duration of analgesia of 6.3±0.8 hours when using clonidine of 1µg/kg with a mean weight of 60.6±19.4 kg.

In a study conducted by **van Tuijl I et al**[11] authors observed the duration of analgesia to be 55 mins in control group (2.2ml Bupivicaine, 0.5%,heavy) and 129 mins in clonidine group (75µg) which is less than that in our study. This could be probably due to the study in pregnant women in whom there is rich vascularity in the spinal cord which can absorb the study drug to circulation very fast and gets eliminated and also due to the lesser mass of drug (11 mg Bupivacaine) used.

The mechanism of clonidine induced potentiation of sensory block in spinal anaesthesia is reported to be mediated by presynaptic (inhibition of transmitter release) and post-synaptic (enhancing hyperpolarisation) affects.

Clonidine is known to increase sensory blockade of local anesthetics and has potent antinociceptive property. Combination of clonidine with a local anesthetic improves the quality of postoperative analgesia and improves immediate post-operative pain scores and prolongs time to the first analgesic request. Analgesia was significantly improved during surgery.

MOTOR BLOCKADE

Time taken for maximum motor blockade and grade of motor blockade: The mean time taken for maximum motor blockade in our study, 7.70±1.12 min in Group-C, 9.77±1.87 min in Group-B and 11.63±1.94 min in Group-A (control group). This is statistically highly significant but, the grade of motor blockade in the three groups did not differ. All the groups had a motor blockade of Bromage grade 3 or 4. This is consistent with the studies done by **Strebel S et al**[8], **Sethi BS et al**[7] **and Saxena H et al**[12] who observed the complete motor blockade of the lower extremity in all patients.

Duration of motor blockade: In our study, duration of motor blockade is taken as the time required for recovery of complete power of lower limbs (Bromage grade 0) from the time of induction of spinal anaesthesia. In our study, the mean duration of motor blockage is 165.66±18.55 min. in control group-A, 176.70±12.91 min. in Group-B and 227.87±22.49 min. in Group-C, which is statistically highly significant. Our study almost concurs with the study conducted by **Kaabachi O et al**[13] who observed the mean duration of motor blockade to be 252±79mins when using clonidine of 1µg/kg and it is more when compared to the study conducted by **Sethi BS et al**[7] who observed it to be 205 mins when using clonidine 1 µg/kg.

Intrathecal clonidine alone even in doses upto 450 µg, does not induce motor block or weakness. In contrast intrathecal clonidine combined with local anesthetics significantly potentiates the intensity and duration of motor blockade. The explanation could be that α-2 adrenergic agonists induce cellular modification in the ventral horn of the spinal cord (motor neuron hyperpolarisation) and facilitates local anesthetic action.

HEMODYNAMIC EFFECTS

MEAN ARTERIAL BLOOD PRESSURE: In the Group-A (control group) the basal value of mean MAP is 94.4±3.42 mmHg and we observed a fall in mean MAP, mainly 15 min to 40 min, which is maximum of 13.63mmHg from mean basal MAP at 20th min (14.44% fall from basal MAP). In the Group-B (clonidine 25 µg) the basal value of mean MAP is 91.87±4.59 mmHg and we observed a fall in mean MAP which is maximum of 21.04 mmHg from mean basal MAP at 60th min (22.90% fall from basal MAP). In the Group-C (clonidine 50 µg)

the basal value of mean MAP is 92.60±5.40 mmHg and we observed a fall in mean MAP which is maximum of 22.10 mmHg from mean basal MAP at 60th min (23.87% fall from basal MAP).

A small dose of intrathecal clonidine is not usually associated with systemic side effects such as bradycardia, hypotension, or sedation. Animal studies have provided evidence of a biphasic effect on blood pressure after intrathecal clonidine. Since, Clonidine is mixed α-1 and α-2 adrenergic agonist at high doses clonidine cause peripheral vasoconstriction, which results in a U – shaped hemodynamic dose-response curve. Accordingly, studies using very low doses intrathecal Clonidine such as 15 to 30 µg found no hemodynamic instability, Most of the studies using 37.5 µg to 150 µg reported significant hypotension and bradycardia, while with higher doses of 300 and 450 µg, relative hemodynamic stability was observed, suggesting a pressor effect on peripheral vessels.

The hemodynamic stability of our patients was better maintained in 25 µg Clonidine group than the 50 µg comparing the number of patients who needed a vasopressor. This was similar to the findings of **Dobrydnjov et al**[10] where only one patient each in 15 µg and 30 µg groups needed vasopressor or Atropine.

Niemi et al[9] used 3 µg /kg of clonidine added to 15 mg of 0.5% Bupivacaine for knee arthroscopy, and reported significant hypotension in clonidine groups their values for mean arterial pressure were also significantly lower than control group after 45 min to 6 hrs.

Hypotension was less pronounced after intrathecal than oral clonidine. Hemodynamic disturbances resulting from intrathecal clonidine depends on other factors also like segmental site of injection, patient position, preloading and baricity of local anesthetic employed.

PULSE RATE:

Clonidine decreases heart rate by a presynaptic mediated inhibition of nor-epinephrine release and by direct depression of atrioventricular nodal conduction. Maximum reduction of mean arterial blood pressure in individual patients occurred within one hour after intrathecal clonidine administration.

In the control group (Group-A) the basal value of mean pulse rate is 81.80±7.03 per min and we observed a decrease in mean pulse rate which is maximum of 7.93 per min from basal value at 20th min (09.69 % decreases from basal value). In the clonidine 25 µg group (Group-B), the basal value of mean pulse rate is 83.53±5.62 per min and we observed a decrease in mean pulse rate which is maximum of 12.70 per min from basal value at 60th min (15.20% decreases from basal value). In the clonidine 50µg group (Group-C), the basal value of mean pulse rate is 80.17±5.11 per min and we observed a decrease in mean pulse rate which is maximum of 19.50 per min from basal value at 60th min (24.32% decreases from basal value) and maximum in all the three study groups. In our study, we noticed a delayed decrease of heart rate in the clonidine groups compared to the control group.

In a study conducted by **Kaabachi O et al**[13], the authors observed the incidence of bradycardia to be 30% in clonidine (2 µg/kg) group which is higher compared to our study and this may probably due to larger dose of clonidine (2µg/kg) used when compared to our study.

SEDATION: In our study sedation is assessed using 'four-point verbal rating scale' from 15 min after intrathecal injection of drugs to 06 hours and maximum sedation in the study duration noticed. No other sedative premedication is given for any of the patients all the three groups and preoperatively also no sedation is given for any of the patients in either group. In our study, in control group (Group-A) five patients (16.67%) found with grade-1 sedation score, it may due to sudden pain relief after spinal anaesthesia. In Group-B (clonidine amount 25 µg) four patients (13.33%) found with sedation score-1 and one patient (3.33%) found with grade-2 sedation score. In Group-C (clonidine amount 50 µg) two patients (6.67%) found in grade-3, three patients (10%) found in grade-2 and seven patients (23.33%) found in grade-1.

In a study conducted by **Saxena H et al**[13], higher incidence of sedation was seen in the clonidine group (37.5 µg) compared to our study. The authors found 90% of the patients were asleep but arousable in the clonidine group (37.5µg). In a study conducted by **Strebel S et al**[8], there was no significant difference in sedation scores among the groups.

Clonidine produces dose-dependent sedation over the dose range 50-900 µg of rapid onset (<20 min) regardless of route of administration. Sedation commonly accompanies the use of clonidine for regional anaesthesia, consistent with the known sedative/anesthetic sparing properties of α-2 adrenergic agonists by action in the locus ceruleus. This brain stem nucleus is associated with a wide variety of physiologic regulatory process, including regulation of sleep and wakefulness and is inhibited by α-2 adrenergic agonists via a G-protein mediated mechanism that involves inhibition of adenylate cyclase.

Nausea and vomiting was observed in few patients of all groups, 3.33% in Group-A and 10% in Group-B and Group-C both. Receptors α-2 adrenergic agonists alone do not induce profound respiratory depression, even after massive overdose. Respiratory rate was monitored to detect respiratory depression and there was no evidence of respiratory depression.

SUMMARY AND CONCLUSION

We conclude that intrathecal administration of preservative free clonidine 25 mcg and 50 mcg along with 0.5% Bupivacaine significantly prolongs the duration of sensory and motor blockade. Significant prolongation of post-operative analgesia occurs with 50 mcg clonidine. Patients with 50 mcg clonidine remains calm, comfortable, minimally sedated throughout procedure with easily arousable with minimum hemodynamic instability like hypotension and bradycardia which can be easily managed.

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