

Prolongation of Spinal Analgesia by Adding Intrathecal Alpha Agonist-Clonidine-Prospective Randomized Study

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Abstract

Clonidine, an alpha-2-adrenergic agonist, have a clinically relevant analgesic action but also a hypotensive action, when administered spinally. In this study, therefore, the analgesic, hemodynamic effects of intrathecal clonidine were studied in patients undergoing lower abdominal and lower limb surgery under spinal anaesthesia. Sixty patients of ASA I-II were randomly divided to two groups. One group received clonidine 15 µg mixed with 15.5 mg 0.5% bupivacaine and the other group an identical saline volume mixed with bupivacaine as above, in a double-blind fashion. Onset and duration of sensory and motor block, blood pressure, heart rate and sedation were followed during and after the operation. The duration of sensory analgesia (regression of the block to L2) was longer in the clonidine group (mean 178 min) than in the control group. Duration of motor blockade was also longer in the clonidine group compared to the control group. Mean arterial pressure and heart rate were significantly lower in the clonidine group compared to the control group. Postoperative the clonidine patients needed less doses of diclofenac sodium than those in the control group. More patients in the clonidine group were sedated 3-4 hr than control group ($p < 0.05$). Addition of clonidine prolonged the bupivacaine spinal block.

Keywords: Clonidin; Bupivacaine spinal block alpha-2-adrenergic agonist.

Introduction

Local anesthetics are the commonest agents used for spinal anesthesia, but their relatively short duration of action may lead to early analgesic intervention in the postoperative period.^{1,2} A number of adjuvants to local anesthetics have been used intrathecally to prolong the intraoperative as well as postoperative analgesia.³ Opioids are commonly used as intrathecal adjuvants to improve the quality of intraoperative analgesia and prolong it in the postoperative period without significant motor or autonomic blockade. However, side effects such as pruritus, nausea, vomiting, urinary retention, and delayed respiratory depression have prompted further research toward non-opioid analgesics with less serious side effects.⁴

Clonidine, a selective partial alpha-2 adrenergic agonist, is being extensively evaluated as an adjuvant to intrathecal local anesthetics and has proven to be a potent analgesic free of opioid-related side effects.⁵ It is known to increase both sensory and motor blockade of local anesthetics.⁶

Intrathecal clonidine has been used as an adjuvant to local anesthetics in various surgical procedures without any clinically significant side effects.^{7,8} Previous studies have described the use of Clonidine in a wide range (15–150 µg).^{7–10}

The aim of the present study was to evaluate and compare the effect of 15 µg of clonidine added to 15.5 mg of hyperbaric bupivacaine, with respect to duration of sensory block and motor block, adequacy of analgesia, and associated side effects if any.

Materials and Methods

The study was approved by the hospital ethical committee, and written informed consent was obtained from all patients. Sixty patients of either sex in the age group of 18–50 years belonging to American Society of Anesthesiologists (ASA) physical status I or II and scheduled for lower abdominal and lower limb surgery were included in the present study. Exclusion criteria were patient's refusal, any contraindication to spinal anesthesia, pregnant patients, patients for emergency surgeries; those with conditions that preclude spinal anesthesia were excluded from the study. This study was prospective double-blind randomized study.

All Patients were allocated into two groups ($n = 30$ each)

Group BC: Patient received 3.5 ml of hyperbaric bupivacaine 0.5% along with clonidine 15 mcg (total volume of 3.6 ml).

Group B: Patient received 3.5 ml hyperbaric bupivacaine 0.5% with 0.1 ml of normal saline (total volume of 3.6 ml)

The study drug was prepared by anesthesiologist who was not involved in the study. All patients were examined preoperatively, and details regarding clinical history and general physical examination were recorded. During the preanesthetic visit, every patient was familiarized with linear visual analog scale (VAS 0 = no pain and 10 = worst imaginable pain).¹¹ Patients were kept fasting for 8 hr and premeditated with oral alprazolam 0.5 mg previous night.

In the operating room, after the establishment of intravenous (IV) line and attachment of standard monitors like non-invasive blood pressure (NIBP), electrocardiography (ECG), and pulse oximetry (SpO₂), preloading was done with 10 ml/kg

body weight of lactated Ringer's solution. Vital parameters heart rate, systolic/diastolic blood pressure, SpO₂ recorded.

All patients were premeditated with Ranitidine 50 mg I.V, and Ondansetron 4 mg I.V. Subarachnoid block was performed using a 25G Quincke spinal needle with the patient in lateral decubitus position at the L3-L4 interspace and the study drug injected. Patients were then turned supine. The time of onset of sensory blockade noted and was taken from time of injection of the drug into the subarachnoid space to loss of pinprick sensation and reassessed every 5 min for 30 min to record the highest level of block achieved.

The time of onset of motor blockade noted and was taken from the time interval between injection of drug into subarachnoid space to onset of Grade I motor block of Bromage scale. The time to achieve maximum motor blockade was noted. Duration of motor block was recorded from onset time to time when the patient was able to lift the extended leg. Thereafter, reassessment was done every 15 min to note two-segment regressions and then every 30 min till the recovery to L3 dermatome. Degree of motor block was assessed by modified Bromage scale as follow.¹²

0. Full flexion of knees and feet.
1. Just able to flex knees, full flexion of feet.
2. Unable to flex knees, but some flexion of feet possible.
3. Unable to move legs or feet.

The side effects of intrathecal clonidine like nausea and vomiting, bradycardia, hypotension, sedation, and others were noted. Rescue analgesia in the form of diclofenac sodium 75 mg intramuscularly was administered whenever VAS was >4.¹³ The time to rescue analgesia (time to first analgesic request) was noted.

Hemodynamic parameters of the patient before the block (basal), every 5 min after the block for 30 min, every 15 min till 2 h, and then every 30 min until 6 h after the intrathecal administration were recorded. Any episode of hypotension or bradycardia in 24 h was noted. Hypotension was defined as a 20% reduction in systolic blood pressure from the baseline value. Mephentermine 3 mg IV stat was administered to treat hypotension and atropine 0.3 mg IV was administered when the heart rate dropped <20% of the basal value. After the completion of surgery, patients were shifted to recovery and further observed for any side effects for the period of 24 hr. The results were analyzed using

IBM SPSS v 20, and independent samples *t*-test was used for the comparisons between the two groups. Chi-square test was used for the analysis. *p* value of <0.05 was considered statistically significant.

Results

Average age of the subjects in Group BC was 35.97 ± 9.593 S.D. and in Group B was 34.63 ± 9.782 S.D. (Fig. 1).

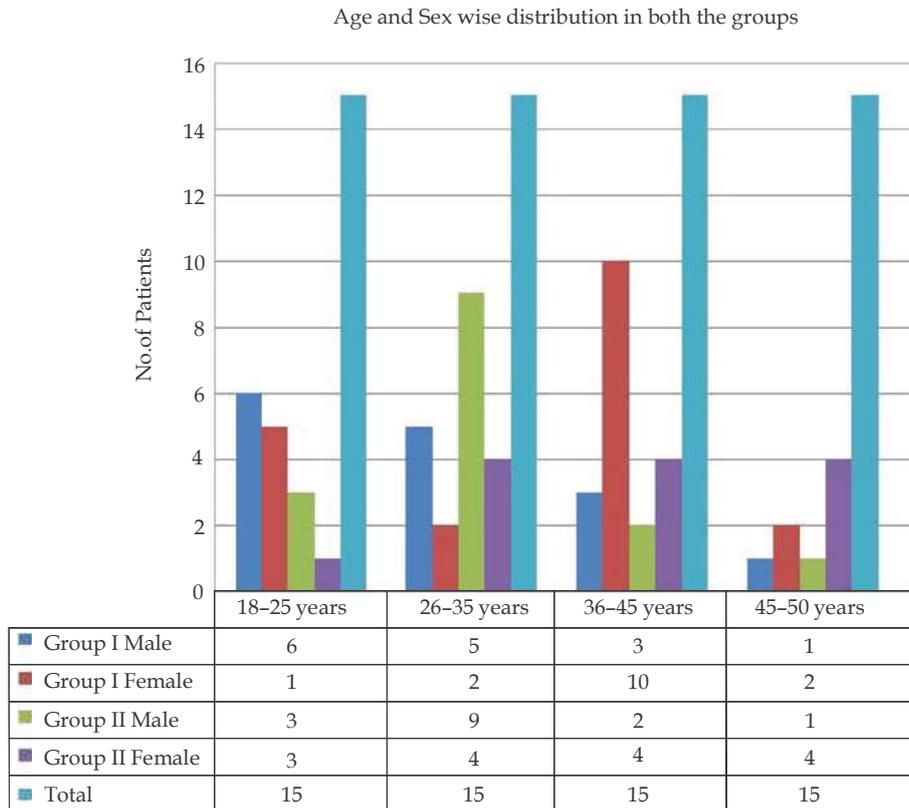


Fig. 1: Comparison of age distribution between the two groups

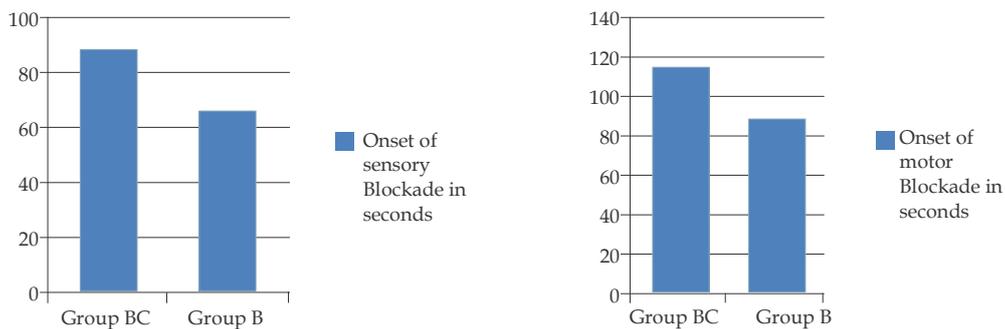


Fig. 2: Onset of sensory and motor blockade (seconds) in either groups

Onset of sensory and motor blockade (seconds) in Group BC was 88.5 and 115.67 sec and in Group B was 66.67 and 89.5 sec respectively. By using 2

independent sample *t*-test *p*-value < 0.001 which is highly significant (Fig. 2).

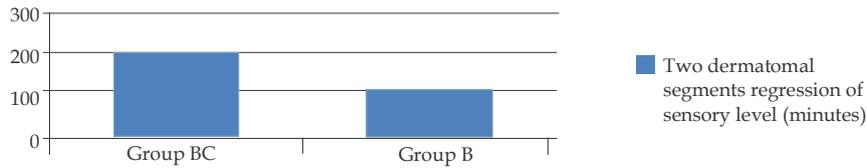
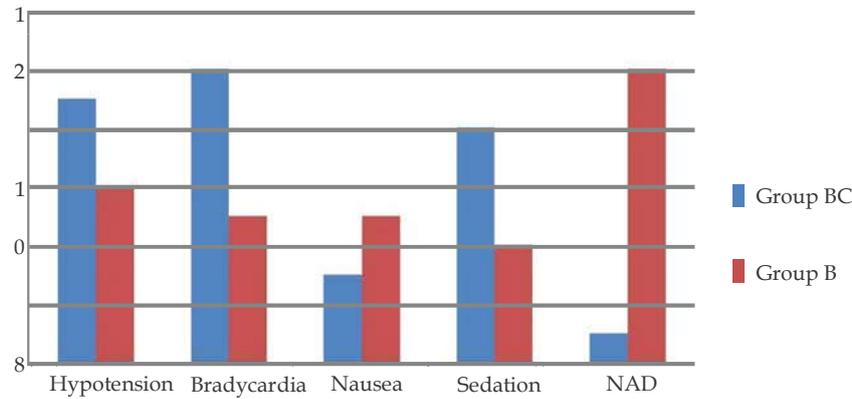


Fig. 3: Comparison of two dermatomal segments regression of sensory level (minutes).



Adverse Effects	Group BC	Group B
Hypotension	9	6
Bradycardia	10	5
Nausea	3	5
Sedation	8	4
NAD	1	10

Fig. 4: Comparison of adverse effects in the two groups

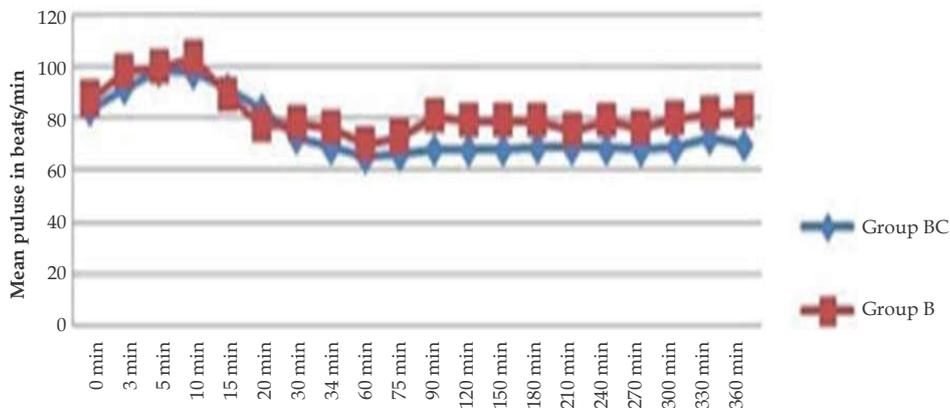


Fig 5: Perioperative mean heart rate of the patients in both the groups at different time intervals.

The mean time for two dermatomal segments regression of sensory level (minutes) in Group BC and Group B was 178 and 118 respectively. By using independent sample *t*-test *p*-value < 0.0001 which was highly significant (Figs. 3 to 5).

Discussion

Clonidine is a selective partial agonist for alpha-2 adrenoreceptors. Its analgesic effect is mediated spinally through activation of post-synaptic

alpha-2 receptors in substantia gelatinosa of the spinal cord. It is known to increase both sensory and motor blocks of local anesthetics by 30–50%. This effect has been reported using doses as high as 1 or 2 µg/kg. At these doses, improved analgesia is associated with systemic side effects such as sedation, bradycardia, and hypotension.⁸ This study compared whether addition of a small dose clonidine to hyperbaric bupivacaine for spinal anesthesia increased the duration of sensory block, duration of motor block, and time to first analgesic request with minimum side effects. Dobrydnjov

et al. added 0, 15, or 30 µg clonidine to 6 mg of intrathecal hyperbaric bupivacaine for inguinal hernia repair and found increase in duration of motor block (146, 155, and 182 min, respectively) as in our study.¹⁴ The mean time to two-segment regression, regression to L2 dermatome, and time to first analgesic request was significantly more in clonidine groups than in control group. Intrathecal clonidine when combined with local anesthetic significantly potentiates the intensity and duration of motor blockade possibly due to the fact that alpha-2 adrenoreceptor agonists induce cellular modification in the ventral horn of the spinal cord and facilitate the local anesthetic action, and prolongation in sensory block can be due to vasoconstrictive effect of clonidine.¹⁴ A significant fall was observed in the arterial blood pressure after intrathecal clonidine administration in our study. The fall in blood pressure occurred at 20–240 min after spinal injection in groups BC than in Group B. Dobryndjov et al. also recorded a significant decrease in MAP 45–120 min after spinal injection in groups BC15 and BC30 than in Group B.¹⁵ Grandhe et al. also observed significant decrease in MAP in groups BC1 and BC2 as compared to group B from 45 min to 8 h after intrathecal injection.⁹ Clonidine affects arterial blood pressure in a complex manner because of opposing actions at multiple sites. The alpha-2 adrenergic agonists produce sympatholysis and reduce arterial blood pressure through effects at specific brainstem nuclei and on sympathetic preganglionic neurons in the spinal cord, effects that are counteracted by direct vasoconstriction resulting from the alpha-2 adrenergic agonists on the peripheral vasculature. Combining alpha-2 adrenergic agonists with local anesthetic can potentially increase the degree of sympatholysis and the resulting hypotension.¹⁷ Heart rate did not change significantly. Postoperative pain relief was better and prolonged in patients receiving intrathecal clonidine as compared to plain bupivacaine in our study. Although De Kock et al. recommended a dose of 15–45 µg of clonidine as optimal for supplementing spinal anesthesia.¹⁵ Dobryndjov et al. noted postoperative nausea and vomiting in four patients (one each in group B and BC15 and two patients in BC30).¹⁴ Sethi et al. observed that one patient in the control group and three patients in the clonidine group had nausea.⁸ Sedation is another central effect of alpha-2 adrenergic agonists that can occur after their administration via systemic, epidural, or intrathecal routes. The sedative effect of clonidine is dose dependent

and thus explains the presence of sedative effects in our study. Dobryndjov et al.¹⁴ and Grandhe et al.⁹ reported similar findings. Niemi et al. and Acalovschi et al. observed significant sedation in patients receiving clonidine because they used higher doses of clonidine.^{10,17} In the study by Sethi et al., 11 patients complained of dryness of mouth, but it was statistically not significant. This was possibly because of a large dose of clonidine (1 µg/kg) used in their study.⁸ No patient in our study complained of dryness of mouth.

With the present study we can summarize that intrathecal clonidine potentiates bupivacaine thereby bringing about better quality and longer duration of analgesia, better postoperative outcome with minimum side effects. Thus we can conclude that intrathecal administration of 15 µg clonidine in combination with 0.5% hyperbaric bupivacaine produces better quality of analgesia compared to bupivacaine alone in lower abdominal and lower limb surgeries. The adverse effects observed in the study were not significant in clonidine group. Though clonidine 15 µg was associated with a higher incidence and duration of hypotension and bradycardia.

Summary and Conclusion

The study was conducted to compare the effect of intrathecal hyperbaric bupivacaine 0.5% and hyperbaric bupivacaine 0.5% with clonidine 15 µg in lower abdominal and lower limb surgeries. Sixty patients belonging to American Society of Anesthesiologists (ASA) classification I and II, aged between 18 and 50 years, posted for elective lower abdominal and lower limb surgeries were randomly allocated for the study. Group BC: 30 patients received intrathecal hyperbaric bupivacaine 0.5% (3.5 ml) and clonidine 15 µg (0.1 ml). Group B: 30 patients received intrathecal hyperbaric bupivacaine 0.5% (3.5 ml) and NS 0.1 ml. The study was conducted to compare the effect of intrathecal hyperbaric bupivacaine 0.5% and hyperbaric bupivacaine 0.5% with clonidine 15 µg in lower abdominal and lower limb surgeries. The adverse effects observed in the study were not significant in clonidine group.

References

1. David LB. Spinal, epidural and caudal anesthesia. In: Miller RD, editor. Miller's Anesthesia. 6th ed, Vol. 2. Philadelphia:

- Churchill Livingstone; 2005.pp.1653–83.
2. Local anesthetics. In: Collins VJ, editor. Principles of Anesthesiology. 3rd ed, Vol. 2. Philadelphia: Lea and Febiger 1993.pp.1232–81.
 3. Shetty PS, Picard J. Adjuvant agents in regional anaesthesia. *Anaesth Intensive Care Med* 2006;7:407–10.
 4. Chaney MA. Side effects of intrathecal and epidural opioids. *Can J Anaesth* 1995;42(10):891–903.
 5. Eisenach JC. Overview: First international symposium on α^2 adrenergic mechanisms of spinal anesthesia. *Reg Anesth.* 1993 Jul-Aug;18(4):207–12.
 6. Chiari A, Eisenach JC. Spinal anesthesia: Mechanisms, agents, methods and safety. *Reg Anesth Pain Med* 1998;23:357–62.
 7. Van Tuijl I, van Klei WA, van der Werff DB, 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. *Br J Anaesth* 2006;97:365–70.
 8. Sethi BS, Samuel M, Sreevastava D. Efficacy of analgesic effects of low dose intrathecal clonidine as adjuvant to bupivacaine. *Indian J Anaesth* 2007;51:415–9.
 9. Grandhe RP, Wig J, Yaddanapudi LN. Evaluation of bupivacaine-clonidine combination for unilateral spinal anesthesia in lower limb orthopaedic surgery. *J Anaesth Clin Pharmacol* 2008;24:155–8.
 10. Niemi L. Effects of intrathecal clonidine on duration of bupivacaine spinal anaesthesia, hemodynamic and postoperative analgesia in patients undergoing knee arthroscopy. *Acta Anesthesiol Scand* 1994;38:724–8.
 11. Downie WW, Leatham PA, Rhind VM, et al. Studies with pain rating scales. *Ann Rheum Dis* 1978 Aug;37(4):378–81.
 12. Gammon GD, Starr I. Studies on the relief of pain by counter irritation. *J Clin Invest* 1941 Jan;20(1):13–20.
 13. Connor TO, Abram S. Atlas of pain injection techniques. Edinburgh: Churchill Livingstone 2003.p.125.
 14. 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. *Anesth Analg* 2003;96(5):1496–503.
 15. De Kock M, Gautier P, Fanard L, et al. Intrathecal Ropivacaine and Clonidine for Ambulatory Knee Arthroscopy: A Dose-Response Study. *Anesthesiology* 2001 Apr;94(4):574–8.
 16. Strebel S, Gurzeler AJ, Schneider CM. Small dose intrathecal clonidine and isobaric bupivacaine for orthopaedic surgery: A dose response study. *Anesth Analg* Oct;99(4):1231–8.
 17. Acalovschi I, Bodolea C, Manoiu C. Spinal anaesthesia with meperidine. Effects of added α adrenergic agonists: Epinephrine vs clonidine. *Anesth Analg* 1997 Jun;84(6):1333–9.

