Original Article

Intrathecal clonidine as an adjuvant to hyperbaric bupivacaine in patients undergoing inguinal herniorrhaphy: A randomized double-blinded study

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Abstract

Background: Clonidine is added to intrathecal local anesthetics to improve intraoperative analgesia and to increase the duration of sensory and motor block. Aim of this study was to evaluate and compare the effects of addition of two different doses of clonidine (15 and 30 mcg) to 11 mg hyperbaric bupivacaine in patients undergoing inguinal herniorrhaphy surgery under spinal anesthesia.

Materials and Methods: Seventy-five patients enrolled in the study were randomly divided into three groups of 25 each. Group I patients received 11 mg hyperbaric bupivacaine, whereas groups II and III received 15 mcg and 30 mcg clonidine, respectively, as an adjuvant to 11 mg hyperbaric bupivacaine. The volume of solution was kept constant to 2.4 ml by adding saline wherever needed.

Results: Highest level of sensory block, time to achieve this level, and highest Bromage scale recorded were comparable among the groups. The mean time to two-segment regression, regression of sensory block to L3 dermatome, and mean duration of motor block were the greatest in group III followed by group II and group I. There was significant fall in mean arterial pressure (MAP) in groups II and III as compared to group I ($P = 0.04$). Episodes of hypotension were more in group III than in group II.

Conclusion: 30 mcg clonidine was associated with more incidence and duration of hypotension than 15 μg of clonidine. 15 mcg clonidine added to 11 mg hyperbaric bupivacaine provides better sensory and motor blockade for inguinal herniorrhaphy.

Key words: Adjuvants in spinal anesthesia, intrathecal clonidine, α-2 adrenoreceptors

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 α_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 and 30 mcg of clonidine added to 11 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 informed consent from all the participants was obtained.

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Access this article online	
Quick Response Code:	Website: www.joacp.org
	DOI: 10.4103/0970-9185.105804

Seventy-five 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 inguinal herniorrhaphy were included in the present study. The patients on cardiovascular medications, those with history of hypersensitivity to clonidine or local anesthetics, and those with conditions that preclude spinal anesthesia were excluded from the study. The study was carried out prospectively in a double-blinded randomized manner.

All patients were examined preoperatively, and details regarding clinical history and general physical examination were recorded. All routine investigations were carried out and informed written consent from all the participants was obtained. During the pre-anesthetic 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 6 h and premedicated with oral alprazolam 0.25 mg at the previous night. In the operating room, after the establishment of intravenous (IV) line and attachment of standard monitors [non-invasive blood pressure (NIBP), electrocardiography (ECG), and pulse oximetry (SpO_2)], IV preloading was done with 500 ml of lactated Ringer's solution over a period of 15–20 min. Heart rate and systolic/diastolic blood pressure recorded after preloading were taken to represent the basal readings of hemodynamic parameters.

All the patients were randomly allocated to one of the three groups ($n = 25$ each) and administered 2.4 ml of the coded intrathecal drug. Patients in all the study groups received hyperbaric bupivacaine 11 mg. Group I received only bupivacaine; group II received 15 mcg clonidine with bupivacaine; and group III received 30 mcg of clonidine with bupivacaine. The volume of solution was kept constant to 2.4 ml by adding saline wherever needed. Allocation to one of three combinations was done using sealed coded envelopes. The study drug was prepared by a fellow anesthesiologist who was not involved in the study. Under all aseptic and universal precautions, spinal anesthesia was administered in lateral decubitus position at the L3–L4 interspace and the study drug injected. Patient was then turned supine and 5 min after subarachnoid block, the level of sensory block was assessed by pin-prick method using a 25-G short beveled needle, and reassessed every 5 min for 30 min to record the highest level of block and time taken to achieve the highest level. 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 follows[12]:

I. Free movement of legs and feet
II. Just able to flex knees with free movement of feet
III. Unable to flex knees, but with free movement of feet
IV. Unable to move legs or feet

Motor block was assessed at the same intervals as sensory block. Time to achieve maximum degree of block as per Bromage scale and its regression to Bromage I was noted. Sedation score was also assessed at the same intervals as sensory block [Table 1]. 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. Intraoperative analgesia rescue was not planned in the methodology. Patients who demanded rescue analgesia intraoperatively were not included in the study.

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. Ephedrine 5 mg IV stat was administered to treat hypotension and, whenever needed, atropine 0.3 mg IV was administered when the heart rate dropped to 50 beats/min or <20% of the basal value. After the completion of surgery, patients were further observed for associated side effects if any for the period of 24 h.

Comparison of quantitative data between groups was done by one-way analysis of variance (ANOVA), and independent samples *t*-test was used for the comparisons between the two groups. Chi-square test was used for the analysis of the dichotomous data. Fisher's exact test was not required anywhere. *P* value of <0.05 was considered statistically significant.

Results

Data of all 75 patients enrolled in the study were included in the analysis. The age, weight, height, ASA status, and duration of surgery of the patients were comparable in the three groups [Table 1]. Mean of highest level of sensory block achieved, time to achieve the highest level of sensory block, time to achieve two-segment regression, time to first analgesic

Table 1: Patient characteristics

	Group I	Group II	Group III
Age (years) (Mean ± SD)	32.12 ± 15.29	30.84 ± 8.87	33.16 ± 10.60
Weight (kg) (Mean ± SD)	59.36 ± 8.53	57.72 ± 6.82	54.04 ± 8.63
Height (cm) (Mean ± SD)	165.48 ± 6.95	166.32 ± 7.15	166.40 ± 5.83
ASA I:II	19:6	20: 5	20:5
Duration of surgery (min) (Mean ± SD)	45.00 ± 6.95	50.00 ± 5.25	48.00 ± 7.15

request, regression to L_3 dermatome, time to achieve maximum Bromage scale, highest bromage scale, and duration of motor block were recorded and analyzed [Table 2].

The highest level of sensory block and the time taken to achieve the highest level of sensory block were comparable among all the groups. The mean time to two-segment regression, time to first analgesic request, and regression to L_3 dermatome was significantly less in group I than in groups II and III, but there was no significant difference between groups II and III [Table 2] ($P < 0.05$). Hemodynamic parameters recorded showed significant fall in mean arterial pressure (MAP) in groups II and III as compared to group I at 5, 15, 30, 75, 90, 120, 150, and 210 min intervals [Figure 1] ($P < 0.05$). The MAP was also significantly lower in Group III as compared to Group II at 5, 15, 30, and 75 min [Figure 1] ($P < 0.05$). When the values of MAP at different time intervals were compared to the basal values of the same group, they were found to be significantly decreased in all the groups ($P < 0.05$) [Figure 1]. The incidence of hypotension was not significant between groups I and II, whereas it was significant between groups I and III and groups II and III [Table 3, Figure 2] ($P = 0.00$). Two patients each in groups I, II, and III had bradycardia, but the same was not significant.

Hypotension was not significant between groups I and II, whereas it was significant between groups I and III and groups II and III ($P = 0.000$). Two patients each in groups I, II, and III had bradycardia. When analyzed statistically, no difference was found among the groups. Incidence of shivering, sedation, vomiting, headache, and dryness of mouth recorded in the postoperative period was not significant among the groups [Figure 3].

Discussion

Clonidine is a selective partial agonist for α_2 adrenoreceptors. Its analgesic effect is mediated spinally through activation of post-synaptic α_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 mcg/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 spread and duration of sensory block, duration of motor block, and time to first analgesic request with minimum side effects .

We observed that peak sensory level was comparable among the groups. Our findings were similar to those of the study conducted by Van Tuijl *et al.*[14] who used the same dose of

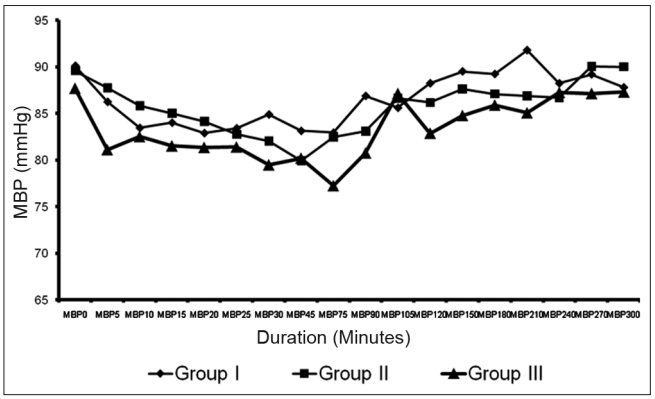

Figure 1: Mean blood pressure recorded at different time intervals after spinal anesthesia

Table 3: Incidence of hypotension and bradycardia

	Group I	Group II	Group III
Hypotension (no of episodes)	4* (4) $P = 0.000$	5 (5)	7$ (12) $P = 0.000$
Bradycardia	2	2	2

**Significant difference between Group I and Group II. $Significant difference between Group II and Group III*

Table 2: Characteristics of analgesia, sensory and motor block

	Group I	Group II	Group III
Highest level of sensory block	T_7 (T_4–T_8)	T_6 (T_4–T_{10})	T_6 (T_4–T_8)
Time (min) to achieve the highest level of sensory block	16.40 ± 4.90	18.40 ± 5.35	18.20 ± 5.38
Time to achieve two-segment regression (min)	72.60 ± 15.42* ($P = 0.00$)	105.60 ± 30.15	110.60 ± 26.22# ($P = 0.00$)
Time to first analgesic request (min)	140.40 ± 36.88* ($P = 0.00$)	223.16 ± 30.76	214.60 ± 46.23# ($P = 0.00$)
Regression to L_3 dermatome (min)	178.80 ± 32.95* ($P = 0.00$)	270.00 ± 39.69	276.00 ± 40.62# ($P = 0.00$)
Time to achieve maximum Bromage scale	16.40 ± 4.90	18.40 ± 5.35	18.20 ± 5.38
Highest Bromage scale	III in 9 patients IV in 16* ($P = 0.004$)	III in 1 patient IV in 24	III in 2 patients IV in 23# ($P = 0.004$)
Duration of motor block	154.20 ± 35.05* ($P = 0.00$)	223.20 ± 45.89	230.40 ± 54.58# ($P = 0.00$)

**Significant difference between Group I and Group II. #Significant difference between Group I and Group III P value <0.05 was considered statistically significant*

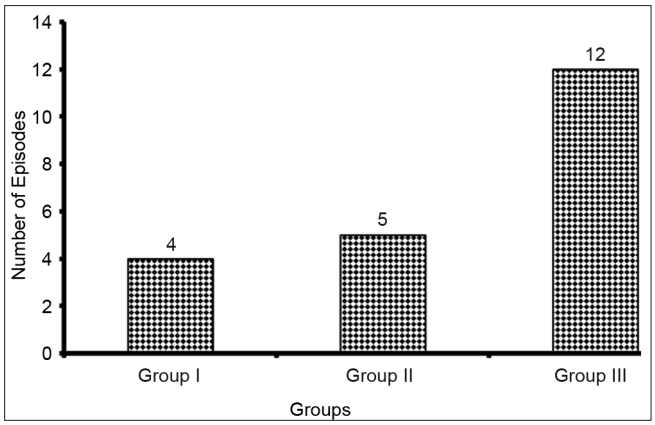

Figure 2: Episodes of hypotension

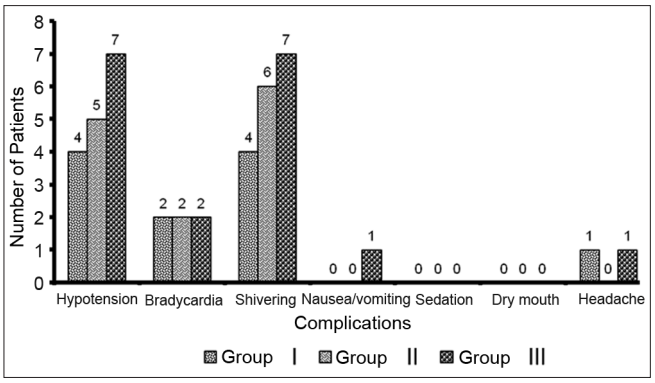

Figure 3: Intraoperative and postoperative complications

clonidine but lower dose of bupivacaine. Peak sensory level in another study showed a similar trend to our study despite the use of large dose of clonidine (1 mcg/kg),[9] suggesting that the dose of intrathecal clonidine does not affect the peak sensory level. Dobrydnjov *et al.* added 0, 15, or 30 mcg 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.[15] The mean time to two-segment regression, regression to L_3 dermatome, and time to first analgesic request was significantly more in clonidine groups than in control group, but increasing the dose of clonidine from 15 to 30 mcg did not affect these parameters. Intensity and duration of motor block was significantly more in groups II and III as compared to group I. Intrathecal clonidine when combined with local anesthetic significantly potentiates the intensity and duration of motor blockade possibly due to the fact that α_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.[15]

Increasing the dose of clonidine from 15 to 30 mcg in our study did not result in any significant difference in peak dermatomal level, peak sensory level, time to two-segment regression and intensity and duration of motor block. De Kock *et al.* also observed that increasing the dose of clonidine from 15 to 45 mcg with 8 mg of ropivacaine did not result in much difference in the above parameters.[16]

A significant fall was observed in the arterial blood pressure after intrathecal clonidine administration in our study. The fall in blood pressure occurred at 15–240 min after spinal injection in groups II and III than in group I. Dobrydnjov *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 mutiple sites. The α2-adrenergic agonists produce sympathicolysis 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 α2-adrenergic agonists on the peripheral vasculature. Combining α2-adrenergic agonists with local anesthetic can potentially increase the degree of sympatholysis and the resulting hypotension.[17] Various clinical studies and our study have shown that as the intrathecal dose of clonidine is increased, the incidence of hypotension also increases. Heart rate did not change significantly in the three groups. These observations are similar to the observations made by Dobrydnjov *et al.*[15]

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,[16] Dobryndjov *et al.*[15] suggested that analgesia significantly increases by 15 mcg of intrathecal clonidine, but increasing the dose further does not increase the duration of analgesia. Our findings are in agreement with the findings of Dobryndjov *et al.*

Incidence of shivering observed in our study is consistent with the observation made by Jeon *et al.* who found that intrathecal clonidine 150 mcg failed to prevent post-spinal shivering and confirmed that IV clonidine 1 mcg/kg is an effective method to prevent shivering in patients undergoing spinal anesthesia for orthopedic surgery.[18] Dobryndjov *et al.* noted postoperative nausea and vomiting in four patients (one each in group B and BC30 and two patients in BC30).[15] Sethi *et al.* observed that one patient in the control group and three patients in the clonidine group had nausea,[8] but it was insignificant in our study. Sedation is another central effect of α2-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 absence of sedative effects in our study. Dobryndjov *et al.* and Grandhe *et al.* reported similar findings. Niemi *et al.* and Aaalovschi *et al.* observed significant sedation in patients receiving clonidine because they used higher doses of clonidine.[10,19] 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 mcg/kg) used in their study.[8] No patient in our study complained of dryness of mouth.

To conclude, the addition of 15 mcg and 30 mcg of clonidine to bupivacaine intrathecal were found to beequally effective in respect of the duration and quality of sensory block, motor block, and time to first analgesic request. Clonidine 30 mcg was associated with a higher incidence and duration of hypotension than 15 mcg of clonidine. When prolongation of spinal anesthesia is desired, the preferred dose of clonidine, as an adjuvant to local anesthetics, is 15 mcg, .

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How to cite this article: Thakur A, Bhardwaj M, Kaur K, Dureja J, Hooda S, Taxak S. Intrathecal clonidine as an adjuvant to hyperbaric bupivacaine in patients undergoing inguinal herniorrhaphy: A randomized double-blinded study. J Anaesthesiol Clin Pharmacol 2013;29:66-70.
Source of Support: Nil, **Conflict of Interest:** None declared.