Comparison of Efficacy of Different Doses of Clonidine with 0.5% Bupivacaine for Spinal Anesthesia in Lower Limb Orthopedic Surgeries

ABSTRACT

Clonidine, a centrally acting α2 adrenergic agonist has been under use as an adjuvant with hyperbaric bupivacaine for prolonging analgesia and maintaining hemodynamic stability during lower limb orthopedic and lower abdominal surgeries.

The purpose of our study was to compare the efficacy and safety of intrathecal Clonidine 50 and 75 μg as adjuvant to hyperbaric Bupivacaine 15 mg (3 mL), and hyperbaric Bupivacaine 3 mL with saline 0.5 mL for onset and duration of anesthesia, hemodynamic stability, and side effects if any.

This prospective randomized controlled study was conducted on 120 patients scheduled for lower limb orthopedic surgeries under spinal anesthesia. The study population was divided into three groups with 40 patients in each group. Group I (controlled group) received 3 mL (15 mg) of 0.5% Bupivacaine heavy and 0.5 mL of normal saline. Group II received 50 μg of clonidine followed by Bupivacaine 0.5% 3 mL (15 mg) and group III received 75 μg of clonidine followed by Bupivacaine 0.5% 3 mL (15 mg) intrathecally. Time taken for onset of sensory and motor blockade, duration of anesthesia, and any perioperative and postoperative complications was noted.

We found that clonidine 75 μg given prior to bupivacaine, 3 mL, significantly prolongs the duration of anesthesia with minimal changes in hemodynamic parameters and postoperative complications.

Keywords: Adjuvants, Bupivacaine heavy, Clonidine, Orthopedic surgeries, Spinal anesthesia.

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INTRODUCTION

Spinal anesthesia is the most commonly employed regional anesthesia technique for lower abdominal and lower limb orthopedic surgeries. Analgesia and anesthesia are provided by the local anesthetics. Bupivacaine is short lived and lasts from 120 to 200 minutes. Several drugs have been tried as adjuvants to bupivacaine to prolong analgesia and anesthesia. Clonidine, a selective alpha-2 adrenergic agonist, has been shown to prolong the sensory blockade and reduce the local anesthetic requirement and also reduction in postoperative analgesic requirement. It has been tried in different doses from 15 to 200 μg either as adjuvant with different local anesthetics or sole anesthetic given intrathecally.1-13

In our study, we looked into the safety and efficacy of two doses of clonidine, 50 and 75 μg given intrathecally as adjuvant, prior to hyperbaric Bupivacaine 0.5% administration in separate syringes, compared with injection hyperbaric Bupivacaine 0.5% 15 mg (3 mL) + 0.5 mL of normal saline given intrathecally. This was done with the view that mixing of these drugs changes the density of both the drugs affecting their spread in the cerebrospinal fluid.14-16

MATERIALS AND METHODS

After obtaining the Institutional Ethical Committee approval, this randomized double-blind study was conducted in our Anesthesia Department.

For the study, 120 patients between 20 and 70 years of age group belonging to American Society of Anesthesiologist (ASA) 1 and ASA 2 status undergoing lower limb major orthopedic surgeries, except replacement surgeries, were recruited. They were randomly divided into three groups of 40 patients each, using thick envelop method. Group I received plain bupivacaine heavy 0.5% 3 mL (15 mg) along with 0.5 mL of normal saline as adjuvant, group II received bupivacaine heavy 0.5% 3 mL with clonidine 50 μg as adjuvant, group III received bupivacaine heavy 0.5% 3 mL with clonidine 75 μg as adjuvant for spinal anesthesia.

Patients having local infection at the injection site, spinal deformities, coagulopathies, hypersensitivity to drugs to be used, cardiovascular, renal, neurological and psychiatric disorders, patients on alpha adrenergic antagonists, Ca+ channel blockers, angiotensin converting enzyme inhibitors, and those who refuse to give written consent were excluded from the study. Patient as well as the anesthesiologist administering spinal...
anesthesia and recording the parameters were blinded about the study drug used.

All the patients underwent preanesthetic evaluation on the previous day and Tab. Alprazolam 0.25 mg was given orally on the night before surgery and kept nil orally for a minimum of 8 to 10 hours. On the day of surgery, patients were cannulated with 18G intravenous (IV) cannula and secured. Ringer's lactate IV fluid was started at the rate of 15 mL/kg/hour. Injection Ondansetron 4 mg and Ranitidine 50 mg was given slowly through IV Basal heart rate (HR), noninvasive blood pressure, oxygen saturation, and electrocardiogram were recorded. Spinal anesthesia was administered under strict aseptic precaution at L3-L4 or L4-L5 space using 25G Quincke spinal needle. After obtaining clear and free flow of cerebrospinal fluid, normal saline 0.5 mL, in group I, clonidine 50 μg in group II, clonidine 75 μg in group III were administered with a separate syringe just before injecting bupivacaine 15 mg (3 mL). Time taken for onset of sensory block was checked with cold gauze at L3 level and was taken as the time interval between intrathecal (IT) injection and loss of sensation to cold at the level below the umbilicus (L3). Time taken for onset of motor blockade was taken as interval between IT injection to Bromage scale 1 (patient is just able to move the limb at hip joint), and time for complete block was taken as interval between IT injection and the complete loss of sensation and unable to move both the lower limbs (Bromage IV). Level of anesthesia was assessed by pinprick method. Duration of sensory block was taken as the interval between IT injection and two-level regression of block from the initial level. Duration of motor block was taken from onset of motor blockade to when the Bromage scale was 2 (patient was just able to move the ankle but unable to flex or move at the knee joint). Total duration of anesthesia was taken as time between the IT injection and complete recovery of sensory and motor blockade (Bromage scale 0). The duration of analgesia was defined as time interval between IT injection and first request for rescue analgesic by the patient. The highest level of sensory block was assessed by pinprick method. Injection diclofenac 3 mg/kg intramuscularly was used as postoperative analgesic.

Hemodynamic parameters like HR, systolic blood pressure (SBP), diastolic blood pressure, mean arterial pressure (MAP) were recorded at 5, 10, 20, 30, 60, 90, 120, 150, 180, 240, 300, and 360 minutes after spinal anesthesia. Loss of blood more than 500 mL was substituted with transfusion of packed red blood cells or additional fluid (Ringer's lactate) depending on the preoperative hemoglobin concentration. Any drop in SBP below 80% of the basal value, not responding to additional fluid of 300 mL, was considered as hypotension, and treated with Injection Ephedrine 6 mg bolus. Bradycardia was defined as HR <50/minute and treated with aliquots of Injection Atropine 0.3 mg bolus.

Any postoperative complications like nausea, vomiting, sedation, and hypotension were recorded and treated accordingly.

**RESULTS**

All the data collected were analyzed using Statistical Package for the Social Sciences version 15.0, SAS 9.2, Stata 10.1, R environment version 2.11.1 software. Analysis of variance (ANOVA) has been used to find the significance of study parameters between the groups. Chi-square/Fisher's exact test has been used for analyzing categorical data. Significance was assessed at 5% (p < 0.05) level of significance.

All the groups were comparable with no significant differences in the demographic characteristics like age, weight, and ASA grading.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of sensory blockade (minutes)</td>
<td>3.93 ± 1.00</td>
<td>3.83 ± 0.96</td>
<td>3.68 ± 0.62</td>
<td>0.439</td>
</tr>
<tr>
<td>Onset of motor blockade (minutes)</td>
<td>7.13 ± 0.88</td>
<td>7.00 ± 0.82</td>
<td>6.88 ± 0.91</td>
<td>0.441</td>
</tr>
<tr>
<td>Time taken for complete block in minutes</td>
<td>22.55 ± 1.80</td>
<td>18.53 ± 1.92</td>
<td>16.80 ± 1.16</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Duration of surgery (minutes)</td>
<td>171.85 ± 42.13</td>
<td>133.80 ± 11.98</td>
<td>147.93 ± 16.16</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

*Moderately significant (p-value 0.01–0.05)
A trend of fall in MAP was observed in all the groups between 20 and 120 minutes. The fall was more in groups II and III than in group I (Table 3). But only three patients in group I, five patients in group II, and eight patients in group III required vasopressor (Ephedrine 6 mg bolus), while others responded to only fluid management for hypotension (Table 4).

Duration of sensory block was 189.55 ± 6.05 minutes in group I, 206 ± 6.69 minutes in group II, 234.40 ± 8.59 minutes in group III with a p-value of <0.001, which was statistically strongly significant, and motor blockade was 202.10 ± 6.55 minutes in group I, 221.05 ± 5.70 minutes in group II, 345.38 ± 7.04 minutes in group III with a p-value of <0.001, which was also strongly significant. Total duration of analgesia was significantly prolonged in group III when compared with other groups (group I = 208.53 ± 31.07 minutes, group II = 236 ± 98 minutes, group III = 368.90 ± 8.27 minutes with a p-value of <0.001) (Table 5).

Postoperatively, three patients in group I, four patients each in groups II and III had nausea and vomiting, while only one patient had nausea in group II. Two patients each in groups I and II and three patients in group III had shivering, which was statistically significant with a p-value of <0.001 (Table 6).

**DISCUSSION**

Clonidine, an alpha 2 adrenergic agonist, has been used extensively for its sedative and analgesic effects. It reduces the amount of local anesthetic agent required when used...
as an adjuvant during spinal anesthesia and prolongs the duration of analgesia compared with hyperbaric bupivacaine alone. It stimulates central inhibitory alpha 2 adrenoceptors to reduce central sympathetic outflow and norepinephrine release, leading to sedation, anxiolysis, and analgesia. It produces analgesia by depressing the release of C-fiber transmitters and hyperpolarization of postsynaptic dorsal horn neurons. It also prolongs the motor block by binding to motor neurons in the dorsal horn cells in the spinal column.

Many authors in the previous studies have used clonidine from 15 to 200 μg as adjuvant to hyperbaric bupivacaine. But the dose of clonidine as an adjuvant which produces prolonged analgesia with minimal side effects has not been established.

In our study, we have tried to establish the efficacy of clonidine 50 μg (group II) and 75 μg (group III) given as adjuvant just prior to the administration of hyperbaric bupivacaine 15 mg (3 mL) compared with hyperbaric bupivacaine alone (group I) for spinal anesthesia in patients undergoing major lower limb orthopedic surgeries.

Clonidine, when combined with local anesthetic bupivacaine, potentiates the sympatholytic effect through inhibition of central sympathetic outflow and postsynaptic dorsal horn neurons, resulting in hypotension. Smaller dose of clonidine up to 75 μg is not usually associated with systemic side effects like bradycardia, hypotension, or sedation.

We have observed in our study that the onset of sensory and motor blockade was comparable between all the three groups and was not significant with a p-value of 0.439 for sensory blockade and 0.441 for motor blockade. But the time taken for complete block was significantly less in group III with p-value of <0.001. Highest level of sensory blockade was achieved in group III (14 patients) less in group III with p-value of <0.001. Highest level of analgesia was also prolonged in group III compared with other two groups (208.53 ± 31.07 minutes in group I, 236.98 ± 5.59 minutes in group II, and 368.90 ± 8.27 minutes in group III) with p-value of <0.001, which was statistically strongly significant. Mean duration of analgesia in a dose-dependent manner but increasing the dose more than 75 μg also increases the incidences of bradycardia, hypotension, and postoperative sedation.

Previous studies have shown that increase in the dose of IT clonidine from 50 to 150 μg increases the duration of analgesia in a dose-dependent manner but increasing the dose more than 75 μg also increases the incidences of bradycardia, hypotension, and postoperative sedation.1-6

CONCLUSION

Intrathecal clonidine has been known to increase the duration of sensory and motor block with excellent postoperative analgesia. In our study we have found that Injection clonidine 50 and 75 μg given intrathecally prior to Injection bupivacaine 15 mg causes prolonged analgesia compared with bupivacaine alone. Analgesia provided by clonidine 75 μg as an adjuvant to bupivacaine 15 mg significantly prolongs the duration of analgesia with hemodynamic stability compared with 50 μg.

LIMITATIONS

We have not calculated the drug dosage as per the height and weight of the patients which might have given better variations in the hemodynamic response and postoperative complications.

REFERENCES