Intrathecal Clonidine as an Adjuvant to Hyperbaric Bupivacaine: A Dose - Response Study

Sara Mary Thomas¹, Mary Verghese², Melchisedec³

ABSTRACT

Introduction: Clonidine, an α₂ agonist, prolongs the action of local anaesthetic and provides satisfactory postoperative analgesia when administered intrathecally. Study aimed to compare the effects between two doses of clonidine (30 and 60 µg) in terms of hemodynamic profile, duration of analgesia, sensory and motor blockade, when used intrathecally as an adjuvant to 2.5 ml of 0.5% hyperbaric bupivacaine.

Material and Methods: In this prospective, randomised, double blind study, 80 patients of American Society of Anaesthesiologists (ASA) I or II, aged 18 – 55 years, undergoing lower abdominal or lower limb surgery lasting less than 180 minutes were included. Patients were divided into two groups of forty patients each and they received intrathecally, 2.5 ml of 0.5% hyperbaric bupivacaine and either 30 µg of clonidine (Group C30) or 60 µg of clonidine (Group C60). Total volume was made constant by adding normal saline. Haemodynamic parameters, duration of sensory and motor blockade and duration of analgesia were noted. A p value <0.05 was considered significant.

Results: Both groups were comparable with respect to demographic profile and haemodynamic parameters. Duration of sensory block, motor block and analgesia were significantly prolonged in Group C60 as compared to Group C30.

Conclusion: Addition of clonidine to hyperbaric bupivacaine increased the duration of spinal anaesthesia and post operative analgesia in a dose dependent manner with minimal adverse effects.

Keywords: Clonidine, α₂ Agonist, Spinal Anaesthesia, Bupivacaine, Analgesia, Haemodynamics

INTRODUCTION

Spinal anaesthesia is a well-known technique for lower abdominal and lower limb surgeries. It is easy to perform and provides fast onset and effective sensory and motor block. ¹ Adjuvant drugs may be added to the local anaesthetic solution not only to prolong the duration of the block but also to provide postoperative spinal analgesia. ² The α₂ - adrenergic agonist clonidine has the ability to potentiate the effects of local anaesthetics. ³ ⁴ It is being extensively evaluated as an alternative to spinal opioids for the control of pain and has been proven a potent analgesic free of some opioid - related, but not all, side effects. ⁵ This study was undertaken to compare the effects of two doses of clonidine on haemodynamic parameters, duration of analgesia, characteristics of sensory and motor block, when added intrathecally as an additive to hyperbaric bupivacaine.

MATERIAL AND METHODS

After approval from the institutional ethics committee and written informed consent, 80 patients of either sex, belonging to American Society of Anaesthesiologists (ASA) physical status I-II, aged 18-55 years, undergoing lower abdominal or lower limb surgeries lasting less than 180 minutes were enrolled in this prospective, randomised, double blind study. Pregnant ladies, patients with any known contraindication for spinal anaesthesia, those with history of allergy to clonidine or local anaesthetics were excluded from the study. All patients received a test dose of clonidine before surgery. Patients were randomly allocated into two groups of forty patients each and they received a total volume of 2.9 ml of coded intrathecal drugs. Group C30 patients were administered 2.5 ml of 0.5% hyperbaric bupivacaine + 30 µg clonidine (0.2ml) + 0.2 ml normal saline intrathecally. Group C60 received 2.5 ml of 0.5% hyperbaric bupivacaine + 60 µg (0.4 ml) clonidine intrathecally. Eighty slips were made in such a manner that forty slips had Group C30 written on it and the other forty had Group C60. The slips were numbered from 1- 80, mixed and kept in a box. One slip was taken and the drug was drawn accordingly and labelled with the number in accordance with the randomization. The slips were coded and the solution was prepared by an anaesthesiologist who was not involved in the study. At the end of the study, decoding was done.

During the pre - anaesthetic visit, patients were instructed about the fasting guidelines and were familiarized with Visual Analogue Scale (VAS) for pain (VAS 0 = no pain and 10 = worst imaginable pain) and were premedicated with Tab Diazepam 5mg one hour prior to surgery. 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 (SpO2)], IV preloading was done with 1 litre of crystalloid over a period of 30 minutes. Under aseptic precautions, lumbar puncture was performed at the level of L3-L4 or L4-L5 intervertebral space using 25G Quincke needle; clear free flowing cerebrospinal fluid (CSF) was identified and the study solution was injected, after which,

1Assistant Professor, Department of Anaesthesia, Dhiraj Hospital, Sumandeep Vidyapeeth, Vadodara, Gujarat, 2Professor and HOD, Anaesthesia, Believers Church Medical College and Hospital, Thiruvalla, Kerala, 3Professor, Anaesthesia, Christian Medical College and Hospital, Ludhiana, Punjab, India

Corresponding author: Sara Mary Thomas, A-20, Maniba Park, Sussen Tarsali Road, Vadodara 390010 Gujarat, India

How to cite this article: Sara Mary Thomas, Mary Verghese, Melchisedec. Intrathecal clonidine as an adjuvant to hyperbaric bupivacaine: a dose - response study. International Journal of Contemporary Medical Research 2018;5(1):12-15.
the patient was turned to supine position and position of operation table was kept horizontal. Data were registered at baseline and every 2 minutes for the first 20 minutes after spinal injection and thereafter every 10 minutes till one hour, followed by every 15 minutes till the end of the surgery. Clinically significant bradycardia and hypotension was treated with IV Atropine and IV ephedrine respectively. Level of sensory block was tested by pin prick method and the highest level of sensory block was noted. Motor block was assessed by Modified Bromage Scale (MBS) as shown in Table 1 and the time taken to achieve complete motor block (MBS=3) was recorded. Patients with inadequate block were excluded from the study. All adverse effects were recorded. Postoperatively, the time for regression of the sensory block to T12 dermatome and full recovery of motor block (MBS=0) were assessed. Duration of sensory block was defined as the time taken from the onset of sensory blockade till regression to T12 level and duration of motor block was defined as the time taken from the onset of motor blockade till return of full motor function. Severity of pain was measured by VAS and the time for the first rescue analgesic was noted. Duration of analgesia was defined as the time from intrathecal clonidine administration to the first request for supplemental analgesia.

STATISTICAL ANALYSIS

Comparison of quantitative data between groups was done by one -way analysis of variance (ANOVA) and unpaired t – test, while paired t- test was used for comparison of quantitative data within a group. Chi-square test was used for the analysis of dichotomous data. p value <0.05 was considered significant. Results of continuous measurements were presented as mean ± standard deviation (sd) and results of cegorical measurements were presented as number (%).

RESULTS

Both groups were comparable with respect to their demographic profile. Haemodynamic parameters recorded showed significant fall in systolic and diastolic blood pressure from baseline at different time intervals in each group, but on comparing the two groups this fall in blood pressure was not significant (p value >0.05). Clinically significant hypotension was readily managed with IV fluids and Ephedrine. 13 patients in Group C30 and 11 patients in Group C60 had bradycardia which was not clinically significant; the difference between the groups was also not statistically significant (p value >0.05). The highest level of sensory block was similar in both groups (p value >0.05) while the mean duration of sensory block was significantly longer in Group C60 as compared to Group C30 (197.63 ± 36.72 minutes and 149.25 ± 24.01 minutes respectively; p value 0.003) Group C60 took less mean time to achieve complete motor blockade as compared to Group C30 (3.48 ± 0.99 minutes vs 6.28 ± 1.75 minutes; p value 0.0005). Mean duration of motor block in Group C60 was 283.13± 57.56 minutes which was longer as compared to Group C30 which was 191.25 ± 25.13 minutes (p value 0.0005). Similarly, mean duration of analgesia was more in Group C60 as compared to Group C30 (354.38 ± 59.20 minutes vs 261.7 5± 33.62 minutes; p value 0.0005).

Characteristics of spinal block are shown in Table 2. There were no difference between the two groups regarding the incidence of side effects like nausea, vomiting and sedation.

DISCUSSION

Our results showed a dose dependent prolongation of sensory and motor block by the addition of intrathecal clonidine. The range of upper level of sensory blockade was similar in both groups. 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 hyperpolarization) effects. Role of vasoconstriction in prolonging sensory block seems to be minor. Intrathecal clonidine alone does not induce motor block but when combined with local anaesthetic significantly potentiates the intensity and duration of motor blockade. Prolongation of motor block could be because of the fact that clonidine induces cellular modification in the ventral horn of the spinal cord (motor neuron hyperpolarisation) and facilitate the local anaesthetic action.

A dose response study done in 80 orthopedic patients, receiving different doses of intrathecal clonidine (37.5 µg, 75 µg and 150 µg) with 18 mg of isobaric 0.5% bupivacaine demonstrated that the patients who received 150 µg clonidine had more intense motor block that resolved after 8-10 hours, which was longer in duration as compared to those who got 75 µg and 37.5 µg clonidine. A dose dependent prolongation of sensory blockade was also seen.

Similar results of prolongation of spinal anaesthesia by intrathecal clonidine were seen in surgeries like knee arthroscopy, lower limb orthopaedic surgeries, gynaecological surgeries and minor surgical procedure like gynaecological surgeries and minor surgical procedure like

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group C 30</th>
<th>Group C 60</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean duration of sensory block(min)</td>
<td>149.25 ± 24.01</td>
<td>197.63 ± 36.72</td>
<td>0.0037</td>
</tr>
<tr>
<td>Mean time taken to achieve complete motor block (Min)</td>
<td>6.28 ± 1.75</td>
<td>3.48 ± 0.99</td>
<td>0.0005</td>
</tr>
<tr>
<td>Mean duration of motor block (min)</td>
<td>191.25 ± 25.13</td>
<td>283.13 ± 57.56</td>
<td>0.0005</td>
</tr>
<tr>
<td>Mean Duration of analgesia (min)</td>
<td>261.75 ±33.62</td>
<td>354.38 ± 59.20</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

Table-2: Characteristics of spinal block

0 = Able to flex the whole lower limb at the hip  
1 = Able to flex the knee but unable to raise the leg at the hip  
2 = Able to plantar flex the ankle but unable to flex the knee  
3 = No movement of lower limb

Table-1: Modified Bromage Scale
The antinociceptive properties of clonidine indicates that it might be useful as an alternative to intrathecal opioids for postoperative analgesia. In our study we observed that 60 µg of clonidine significantly prolonged the duration of analgesia as compared to 30 µg of clonidine. This was in concordance with the results observed in a prospective, randomised, double blind study of 36 parturients who received 50,100 or 200 µg of intrathecal clonidine as the sole analgesic agent during first stage of labor and it was seen that the duration of analgesia was significantly longer in patients who received 200 and 100 µg than 50 µg clonidine. Likewise, another study done to evaluate the analgesic profile of 150,300 and 450 µg doses of intrathecal clonidine in women who underwent elective cesarean section, demonstrated that intrathecal clonidine produced dose dependent and long-lasting analgesia (7±1.3, 10 ±1.3 and 14 ±1.3 hours respectively). As with lipophilic opioids, it is possible to achieve analgesia from systemic, epidural or intrathecal administration of clonidine. However, clonidine is more potent after neuraxial than systemic administration, indicating a spinal site of action and favoring neuraxial administration. Experimental data indicate that the analgesic effects of intrathecally administered α₂-adrenergic agonists are mediated spinally through α₂ adrenoceptors located in the superficial layers of the dorsal horn of the spinal cord. The rationale behind the intrathecal administration of clonidine was to achieve a high drug concentration in the vicinity of the α₂ adrenoceptors in the spinal cord. Clonidine after neuraxial administration affects arterial blood pressure in a complex manner because of opposing actions at multiple sites. In animal studies, it has been demonstrated that intrathecal clonidine at lower doses has a depressor effect on systemic blood pressure, mediated by spinal α₂ adrenoceptors; but has a pressor effect; and produces marked bradycardia, mediated by peripheral α₂ adrenoceptors, when a large dose is administered. As a result, the dose response for neuraxial clonidine on arterial blood pressure in humans is generally considered to be U-shaped. Its haemodynamic effects further depends on the segmental site of injection, the patient’s position, the rate of injection and the temperature of the injected solution. In our study, the fall in systolic and diastolic blood pressure from baseline were comparable in both groups and relative haemodynamic stability was observed. This was consistent with the analysis done by Grandhe et al., in their study, in which, 45 patients were allocated to receive intrathecally 1.5 ml of 0.5% heavy bupivacaine combined with either 1 ml of normal saline or clonidine 1µg/kg or 1.5 µg/kg and it was found that the mean arterial blood pressure showed no significant change from the baseline in any of the groups during the study. The authors hypothesized that when a large dose of local anaesthetic is used, the hypotensive action of clonidine is masked by dense axonal blockade produced by the local anaesthetic. In our study also, we had used a relatively high dose of bupivacaine ie 12.5 mg, which may explain why no significant hypotension was evident on comparing the two groups. Several other investigators have also studied the haemodynamic profile of intrathecal clonidine. Filos et al evaluated the dose response to 150 µg, 300µg and 450µg of intrathecal clonidine and observed haemodynamic stability with 300µg and 450µg doses of clonidine while there was a reduction of arterial blood pressure (systolic, diastolic and mean) with 150 µg of intrathecal clonidine. They reasoned that as clonidine is an α₂ adrenergic agonist, high clonidine doses causes peripheral vasoconstriction which explains the haemodynamic stability with higher doses of intrathecal clonidine.

CONCLUSION

The addition of intrathecal clonidine to hyperbaric bupivacaine dose dependently prolongs sensory block, motor block and duration of analgesia with relative haemodynamic stability and minimal side effects. Hence 60 µg of clonidine is a preffered dose when prolongation of spinal anaesthesia and postoperative analgesia is desired as compared to 30 µg of clonidine.

REFERENCES


Source of Support: Nil; Conflict of Interest: None
Submitted: 25-12-2017; Accepted: 28-01-2018; Published: 06-02-2018