Low Dose Intrathecal Clonidine With Bupivacain Improves Onset And Duration Of Block With Haemodynamic Stability

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Abstract
There are many studies in the literature on beneficial effects of addition of intrathecal clonidine to bupivacain, with different authors using different doses (15 to 300 mcg) of clonidine with satisfactory outcome. Onset time has not been specifically mentioned in most of the studies. We aimed to evaluate the lowest dose of intrathecal clonidine, as adjuvant to hyperbaric bupivacain that will produce maximum benefit with minimum side effects. We studied eighty adult patients belonging to ASA grade I and II, scheduled for below umbilical surgery under spinal anesthesia dividing them randomly into four groups. Control group received 13.5 mg 0.5% hyperbaric bupivacaine (group 1) Study groups received clonidine 15µg, (Group 2) , 30 µg (group 3),and 37.5 µg (group 4) made to 3ml volume with 13.5 mg 0.5% hyperbaric bupivacaine.The mean time from injection to onset of block was lower, while duration of analgesia and motor blockade was longer in all the clonidine groups(most significant in group 4).The changes were less significant or not significant between group 3 and 4. 30% of patients in group 4 as compared to 20% in group 3 had a significant fall in mean arterial pressure and heart rate. 90 % pts were sedated in group 4.

We concluded that addition of clonidine to bupivcaine significantly reduces the onset time with increase in the duration of spinal block as compared to bupivacaine alone with 30 mcg as optimum dose.

ACKNOWLEDGEMENT
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INTRODUCTION
After the discovery of adrenergic pain modulating system in the spinal cord, adrenergic agonists have been used neuraxially for perioperative analgesia. Clonidine prolongs the duration of intrathecally administered local anesthetics and has potent antinociceptive properties. The commonly administered doses produce hypotension and bradycardia. The doses in the range of 150–300 µg were arbitrarily chosen; the optimal dose in adults in terms of effects versus side effects of intrathecal clonidine by itself is controversial. Until recently, only a few studies have focused on small doses (15 to 150mcg) of intrathecal clonidine in surgical patients. Hence in this study, we investigated the effects of clonidine in the dose range of 15 to 37.5 µg, added to 13.5mg , 0.5%, intrathecal hyperbaric bupivacaine, comparing with the effects of bupivacaine alone in patients undergoing surgery below the level of umbilicus, including lower extremity.

METHODS
After approval from the local ethical committee and written informed consent, 80 patients (ASA I–II), scheduled for elective surgery below umbilicus expected to last less than 180 minutes, were included in this prospective double blind study.

The patients were familiarized with the 10 cm visual analogue scale (VAS) for pain during the pre anesthetic visit and informed of the feeling of tingling, warmth or heaviness that may be felt after the injection. Each patient received 1 mg I/v midazolam in the pre op before shifting to OT where all monitoring (ECG, noninvasive blood pressure and SpO2) was established and preloading done with 10 ml kg-1 ringer lactate over 30 min. A midline spinal puncture at L3/4 space in sitting position with 25-gauge Quincke needle was performed. All patients received a coded intrathecal drug volume of 3.0 ml at a rate of 1 ml/ 5 sec with13.5 mg 0.5% hyperbaric bupivacaine, with saline ± clonidine. The control group (group 1) received bupivacain with saline (0.3ml) while study groups (Groups 2–4) received clonidine 15 µg (Group 2), 30µg (Group 3), or 37.5 µg (Group 4) added to bupivacaine in the same syringe. It will be worthwhile mentioning here that the study was planned with 45 µg
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clonidine for group 4 but all initial 5 patients who received this dose had significant sharp fall in pulse and BP needing efipress and atropine. Hence we reduced the dose to 37.5mcg for group 4.

The drug combinations were prepared by one anesthetist and, various observations were made by a second anesthesiologist who was involved after the procedure had been performed.

Time of onset of block was subjectively assessed by patient complaining of a feeling of warmth, heaviness of limbs, or a tingling sensation, objectively confirmed by decreased VAS scores to pinprick to 5 or less at the calf level. Level of sensory block (pinprick test), grade of motor block (Bromage scale Grade I-- Free movement of legs and feet, Grade II - knee flexion, free feet movement, Grade III- no knee flexion, but free feet movement and Grade IV- Unable to move legs or feet), level of sedation(No sedation-0, Drowsiness-1, Asleep but arousable-2, Unarousable with loss of verbal contact-3) and pain score (10 cm VAS) were recorded before the block, every min for 5 min, every 5 minutes until surgery lasted, every 15 min till 3 hrs and later at hourly intervals until 6 hours after the injection. The maximum ascent of sensory blockade, time to achieve sensory block up to T10, regression of block by 2 segments and the duration of analgesia were also noted. IV fluids (crystalloid, colloid or blood) were administered according to blood loss and haemodynamic instability. Haemodynamic instability was defined as a 30% reduction in mean arterial BP from baseline value and was treated with 300 mL of additional fluids and IV ephedrine (6-mg bolus) if required.

Patients were observed in the OT and recovery room for any other side effect and the need for additional medications was recorded. The analgesia time was recorded up to first rescue analgesia requirement, provided by diclofenac sodium 75mg intramuscularly on demand.

The mean and standard deviations for the observed data were calculated and compared with the control and within clonidine groups, using Student’s t-test. A “p”value <0.05was taken as significant and p<0.01 was considered highly significant. The sample size of 20 patients per group was based on the assumption that an increase of 60 min in the duration of spinal anesthesia and an increase of 30% in the time interval from spinal anesthesia to the first request for supplemental analgesia would be detected ( β = 0.05; ß = 0.8), both of which were considered clinically meaningful.

RESULTS
A total of 80 patients were studied with 20 patients in each group. All the groups were similar in respect of age, weight, ASA status and types of surgeries (Table 1)

Figure 1
TABLE 1 : Patient Characteristics

Comparative values (mean± SD) of observed parameters regarding block characteristics are shown in Table 2 with relevant “p” values in Table 3.
The mean time of onset of sensory block was significantly lower (p<0.01) in all the clonidine groups in a dose dependant manner compared to control (group1), lowest in group 4 (0.92±0.08min), group 3 (0.98±0.09min), group 2 (1.48±0.39mn) or group1 (3.95±1.76). The difference in group 2 and 3 as well as group 2 and 4 was also statistically significant (p<0.01 and p<0.05 respectively). How ever there was no significant difference between the values of group 3 and 4.

The mean time of onset of motor block was lowest in group 4 (2.20±0.50min). All clonidine groups (gp2 -2.67±0.50 min, gp3 -2.30±0.45 min) had a significantly quicker onset (p<0.01), as compared to group1 (7.41±0.55 min). The difference was highly significant between group2 and 3 as
well as group 2 and 4 (p<0.01) while it was insignificant between groups 3 and 4.

There was no statistical difference in the extent of block achieved (Table 2) in any group, but it was achieved significantly faster in a dose dependant manner in all clonidine groups (2, 3, 4) (p<0.01) as shown by the mean time to achieve a sensory block to T10 level (2.58min in group 2, 2.54min in group 3, 2.085min in group 4--Table-5) as compared to group 1 (6.57min). The difference was not significant between group 2 and 3 or 3and 4.It was significant at p<0.05 between group 2 and 4.

The duration of sensory block was compared by 2 segment regression time, mean VAS scores at 3.5 hrs and analgesia time. All three criteria had best numerical values in group 4 (table 4). The improvement was highly significant (p<0.01) in all clonidine groups compared to control (group1), and also between Group 2 and 4.the difference was of lower significance (p<0.05) between group 3 and 4. Three patients in group 1 had to be given pentazocine 15 mg intra op after 45 min due to complain of discomfort. No patient in any of the clonidine groups complained of any pain and needed no supplementation.
# Table 4: Haemodynamic parameters

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Pulse</td>
<td>72.0</td>
<td>72.0</td>
<td>72.0</td>
<td>72.0</td>
</tr>
<tr>
<td>Blood</td>
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<td>110.0</td>
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<td>110.0</td>
</tr>
<tr>
<td>Pressure</td>
<td>90.0</td>
<td>90.0</td>
<td>90.0</td>
<td>90.0</td>
</tr>
<tr>
<td>Systolic</td>
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<td>120.0</td>
<td>120.0</td>
<td>120.0</td>
</tr>
<tr>
<td>Diastolic</td>
<td>80.0</td>
<td>80.0</td>
<td>80.0</td>
<td>80.0</td>
</tr>
</tbody>
</table>

Note: The data includes various parameters such as blood pressure, heart rate, and pulse, measured at different time intervals. The values are represented in millimeters of mercury (mmHg) for blood pressure and metric units for other parameters.
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A complete motor blockade of the lower extremities was observed in all patients. The motor block was most prolonged and intense in group 4 as seen by time to return to Bromage 1 (235 ±31.9min) and scores at 3.5 hrs (3.6±0.50). The values were significantly higher (p<0.01) in all the clonidine groups compared to group1 (Table 2, 3). The difference between group 3 and 4 was less significant (p<0.05), while the difference between 2 and 3; 2 and 4 had p values<0.05 and<0.01 for intensity and duration of block.

The haemodynamic parameters (Table 4) were similar in all the 4 groups at any point of time with no statistical variation (Table 3). There was a 20% fall in the mean pressure from the baseline in group 4 as compared to 8% in group 1, 30 min after the injection.

There was no respiratory depression or desaturation in any patient in any group. Eighteen patients (90%) had grade 2 sedation in group 4 as compared to only 8 (40%) in group 3 (Table 5).

**DISCUSSION**

Clonidine is a selective partial agonist for alpha 2-adrenoreceptors. It is known to increase both sensory and motor block of local anesthetic (7). The analgesic effect following its intrathecal administration is mediated spinally through activation of post synaptic alpha -2 receptors in substantia gelatinosa of spinal cord and it works by blocking the conduction of C and A delta fibers, increases potassium conductance in isolated neurons in vitro and intensifies conduction block of local anesthetic (8). Roh et al (9) recently suggested that one of the mechanisms for the enhanced potency of intrathecal clonidine administration in a rat model of neuropathic pain is its ability to modulate spinal cord NMDAR activation via suppression of NR1 phosphorylation.

We observed that addition of clonidine improved the onset time, speed of spread, and duration of block in a dose

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Table 5: Side Effects

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Control</th>
<th>Group 1 (Clonidine 10mcg)</th>
<th>Group 2 (Clonidine 30mcg)</th>
<th>Group 3 (Clonidine 50mcg)</th>
<th>Group 4 (Clonidine 37.5mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seclusion</td>
<td>0</td>
<td>3</td>
<td>15</td>
<td>40</td>
<td>90</td>
</tr>
<tr>
<td>Percentage</td>
<td>0%</td>
<td>15%</td>
<td>40%</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>Significant drop in Respiratory rate</td>
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<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>Percentage</td>
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<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Significant drop in Heart rate</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No of patients</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Percentage</td>
<td>10%</td>
<td>15%</td>
<td>20%</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Significant drop in Blood Pressure</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No of patients</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>6</td>
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</tr>
<tr>
<td>Percentage</td>
<td>10%</td>
<td>20%</td>
<td>20%</td>
<td>30%</td>
<td></td>
</tr>
</tbody>
</table>

Note: Though the numerical values are the same for drop in heart rate and blood pressure, they did not occur in the same patient.
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dependant manner. We valued the subjective sensation of feeling of warmth in lower limbs in all the patients receiving clonidine, which corresponded with decreased VAS score at the calf level. A similar correlation of subjective sensation of swelling after regional blocks has been reported by Paqueron et al. Maximum benefit was seen with 37.5 mcg dose, but 30% of patients had fall in pulse and BP and 90% patients were sedated. The benefits were similar with 30 mcg clonidine with lesser side effects. 15 mcg clonidine also showed significant improvement with negligible side effects but values were significantly lower than the 37.5 mcg group. There was no difference in the maximum level of block achieved.

Regarding onset time, our findings were similar to Filos KS who compared 150, 300 and 450 mcg of clonidine for post op analgesia after elective section performed in GA and found immediate reduction of pain scores with 450 and 300 mcg of clonidine, namely 3rd and 6th min after injection. We observed decreased VAS scores to pinprick almost instantly with 37.5 mcg and 30 mcg dose and all the orthopedic patients reported almost instant reduction (<1min) in pain. A possible explanation could be from the results of the study by Nishiyama et al showing that intrathecally administered combinations of bupivacaine and clonidine produce synergistic analgesic effects on both acute thermal and inflammation-induced pain with decreased side effects. The synergistic potency was higher for inflammatory-induced pain than for thermal-induced pain. Secondly, we used much lower doses and Wolf et al reported that firing frequency of trains of action potentials in Tonically-firing neurons (TFNs) is reduced at low concentrations (10 µM) of clonidine. After a dose of 1 µg kg⁻¹ intrathecally clonidine in humans, the peak CSF level was about 6 µM. These concentrations are within the range required to partially block voltage-gated Na⁺ and K currents and to shift the steady-state inactivation curve to more negative potentials. Heo and young et al had found no difference in the onset time using 150 mcg clonidine.

The spread of block to T10 in our study was quicker in the clonidine groups in a dose dependant manner, contrary to the finding of Grandhe et al who found no such difference. The highest level block was similar in all 4 groups in our study as also reported by Grandhe and Sethi, while Dobrydnjov et al had found a difference of 2 to 4 segments with 30 mcg clonidine on the operated side using a unilateral block.

The duration of sensory block was prolonged in our study comparable to most of the studies. 2 segment regression time was prolonged to almost 200% in our study, much higher percentage than study of Dobrydnjov which can be explained by lower dose and strength of bupivacain used by them. Moreover, the control values of the duration of sensory and motor block were lower in our study as compared to other studies. The prolongation of motor block in our study was comparable to studies of Strebel(Sethi and Grandhe) in spite of higher volume or higher dose of clonidine used by them. This was different from Dobrydnjov et al, who found no prolongation of motor block or Tuji reporting small increase by 25 to 34 min , after using only 6 mg of bupivacain diluted to 3 ml with similar clonidine doses.

Total analgesia time was prolonged in our study similar to Strebel et al, and lesser than Grandhe, and Sethi ET. It was higher than Dobrydnjov et al which is as expected considering the different doses of clonidine or bupivacain used. We found a better quality of block in all 3 clonidine groups where no supplementation with GA for ‘relaxation’ requests from the surgeon, or additional analgesic was needed intra operatively. This was comparable to the results of Dobrydnjov et al who reported the surgeon rating the operating conditions as excellent or good in 93%–100% of patients receiving 15 and 30mcg clonidine with bupivacain.

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 a mixed a₁–a₂-adrenergic agonist, high clonidine doses cause peripheral vasoconstriction, which results in a U-shaped haemodynamic dose-response curve. Accordingly, studies using very low doses intrathecal clonidine such as 15 to 30 mcg found no haemodynamic instability. Most of the studies using 37.5 mcg to 150 mcg reported significant hypotension and bradycardia, while with higher doses of 300 and 450 mcg, relative haemodynamic stability is observed, suggesting a pressor effect on peripheral sites. The haemodynamic stability of our patients was better
maintained in 15 mcg and 30mcg clonidine groups than the 37.5 mcg comparing the number of patients who needed a vasopressor. This was similar to the findings of Dobrydnjov et al (5) where only one patient each in 15 mcg and 30mcg group needed vasopressor or atropine. The average percentage fall from the baseline was also comparable in our study.

We did not see statistically significant hypotension in any clonidine group at any point of time compared to the control which was in accordance with the findings of Strebel 1 and in contrast to the findings of some other authors, like Neimi et al1, Sethi 3, Grandhe et al 14 who used higher doses of clonidine. Niemi used 3 μg.kg-1 of clonidine added to 15mg of 0.5% bupivacaine for knee arthroscopy, Grandhe et al 15 used 1 mcg and 1.5 mcg per kg of clonidine with 1.5 ml hyperbaric 0.5% bupivacaine, and reported significant hypotension in 10% and 8% pts in the two clonidine groups. Their values for MAP were also significantly lower than control group after 45 min to 8 hrs.

Three studies conducted with isobaric bupivacaine and clonidine reported no significant hypotension. The doses used were 75 and 100 μg clonidine with 13.75 mg of 0.5% bupivacaine for knee arthroscopy, Graa et al 16 used 1 mcg and 1.5 mcg per kg of clonidine with 1.5 ml hyperbaric 0.5% bupivacaine. In contrast to the findings of some other authors, like Klimscha et al 2, Bonnet F, Diallo A, Saada M, Belon M, Guibaud M, Boico O. Prevention of tourniquet pain by spinal isobaric bupivacaine with clonidine. Br J Anaesth 1989; 63: 93-6. Strebel S, Jürg A, Gurzeler, Schneider m. c, Aeschbach A, Kindler c h, Small- Dose Intrathecal Clonidine and Isobaric Bupivacaine for Orthopedic Surgery: A Dose-Response Study Anesth Analg 2004;99:1231-1238. Dobrydnjov I, Axelsson K, Thorn SE, et al. Clonidine combined with small-dose bupivacaine during spinal anesthesia for inguinal herniorrhaphy: a randomized double-blind study. Anesth Analg 2003; 96: 1496–503.

In Conclusion, our study has demonstrated that addition of intrathecal clonidine to bupivacaine, even in very small doses, significantly improves the onset and duration of sensory and motor block with relative haemodynamic stability. The 30 mcg dose provides maximum benefit and minimum side effects. It is recommended when prolongation of spinal anesthesia is desired as, for example in patients scheduled for long, lower abdominal and lower extremity orthopedic procedures.

References

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