Evaluation and comparison of intravenous clonidine and intravenous dexmedetomidine on duration of bupivacaine spinal anaesthesia

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Abstract
Context: Alpha-2 agonists improve the block characteristics in regional anaesthesia, when added to local anesthetics.
Aim: To evaluate and compare efficacy of dexmedetomidine and clonidine, as an intravenous adjuvant to intrathecal bupivacaine.
Settings and Design: Prospective, randomized, double-blind placebo-controlled study.
Methods and Material: 75 patients of American Society of Anaesthesiologists status I or II, scheduled for orthopaedic lower limb surgery under spinal anaesthesia, were randomly allocated into three groups of 25 each. Patients in group D received dexmedetomidine 1μg/kg; group C received clonidine 2μg/kg and group PL received physiological saline, each premixed to 20 ml intravenously over 20 min, starting 20 min after the subarachnoid block with 15 mg of 0.5% hyperbaric bupivacaine. Duration of sensory and motor blockade, postoperative analgesia, sedation scores and side effects were recorded.
Statistical analysis used: Parametric testing done using one-way analysis of variance (ANOVA), intergroup comparison with post-hoc analysis Tukey’s test. Categorical data analyzed using Chi-square test. P<0.05 was statistically significant.
Results: Duration of sensory block was significantly prolonged by dexmedetomidine (231.20±24.84 min) and clonidine (200±23.67 min) than placebo (171±12.25 min) (p<0.001). Duration of motor block was 135.20±12.87 min with placebo, 180.40±24.70 min with clonidine and 205.20±25.56 min with dexmedetomidine (p<0.001). Postoperative analgesia was significantly prolonged by dexmedetomidine (255±23.14 min) than by clonidine (221.40±24.30 min) and placebo (202.60±14.08 min) (p<0.001). The mean sedation score was significantly higher in dexmedetomidine group.
Conclusion: Single-dose intravenous dexmedetomidine and clonidine given after spinal anaesthesia prolong duration of sensory and motor block and postoperative analgesia.

Keywords: Clonidine, Dexmedetomidine, Spinal anesthesia.
Key Messages: Alpha-2 agonists prove to be useful intravenous adjuncts to spinal anesthesia. They effectively prolong the duration or both sensory and motor block as well as postoperative analgesia, without any clinically significant adverse effects.

Introduction
Clonidine as well as dexmedetomidine are commonly added to the local anesthetics administered by different routes, including peripheral nerve blocks, intrathecal, epidural, caudal as well as in intravenous regional anaesthesia.1-4 The concurrent injection of alpha-2 adrenergic agonist drugs improves the nerve block characteristic of local anaesthetics through either local vasoconstriction and facilitation of C fibre blockade or spinal action caused by retrograde axonal transport or simple diffusion along the nerve,5-7
Clonidine and dexmedetomidine are selective α-2 adrenergic agonists with some α-1 agonist property. Dexmedetomidine is around eight to ten times more selective at α2 receptors as compared to clonidine.5,8
In our study we have evaluated the effect of intravenous dexmedetomidine and clonidine on duration of motor and sensory block as well as postoperative analgesia, by intrathecal bupivacaine.

Subjects and Methods
We carried out this prospective, double-blind study after approval of the ethical committee of our institute. 75 patients of ASA (American Society of Anaesthesiologists) physical status I and II, of either sex, aged 18-60 years, weighing 50-70 kg, measuring 150-170 cm in height, undergoing orthopaedic lower extremity surgery (plating and nailing for fracture tibia, plating for fracture shaft femur, triple arthrodesis for ankle) under spinal anaesthesia were included. Exclusion criteria were presence of uncontrolled diabetes mellitus, cardiac disease, hypertension, chronic obstructive airway disease, hepatic and/or kidney disease, alcohol or drug dependence, psychological disease, spinal deformities or any condition contraindicating subarachnoid anesthesia, pregnant or lactating females, allergy to amide type of local anesthetics and those on adrenoreceptor agonist or antagonist therapy.

Thorough preoperative assessment was done and a written, valid and informed consent was obtained from all the patients. On arrival to the OT, patients’ baseline heart rate(HR), non-invasive blood pressure(NIBP) and electrocardiogram(ECG) were noted. 18G intravenous cannula was inserted in peripheral vein and patients were prehydrated with 500 ml of lactated Ringer’s solution. Under strict aseptic precautions, lumbar puncture was performed in the L3-L4 interspace via midline, using a 27-G Whitacre needle with the patient in sitting position. Hyperbaric bupivacaine (0.5%), 15 mg was injected in subarachnoid space and the patients...
made supine. Supplemental oxygen was given via a face mask at 5 L/min, throughout the procedure.

The patients were distributed in three groups of 25 patients each, with the aid of a computer generated random number list: group D were administered dexmedetomidine 1 μg/kg, group C were administered clonidine 2 μg/kg and group PL were administered 20 ml normal saline as placebo. The study drug was made to 20 ml of final volume and administered as an intravenous infusion over 20 mins, starting 20 min from the subarachnoid block. The patient as well as anaesthesiologist who performed the procedure, were both blinded to the intravenous drug administered.

The vital parameters, [heart rate (HR/min)], mean arterial pressure (MAP in mm of Hg), oxygen saturation (SpO2 %), respiratory rate (RR/min)] were recorded at 2 min and 5 min from the spinal block and then at 5 min interval thereafter throughout the surgery and every 15 minutes in the postoperative care unit, until the block was completely reversed. The sensory level was checked in mid-clavicular line using pin prick. Modified Bromage scale was used to quantify sensory block. (grade 0: No paralysis, 1: inability to raise the extended leg, 2: inability to flex the knee, 3: inability to flex the ankle). Sensory and motor block was checked at every 15 minutes intraoperatively and postoperatively. Duration of sensory block was defined as the time for sensory block to regress to S1 dermatomal level. Motor block duration was defined as the time for the block to regress to Bromage scale 0.

The level of sedation was assessed at 15 min intervals using Ramsay Sedation Scale (RSS) intraoperatively and post-operatively (1: Anxious or agitated; 2: Co-operative and tranquil; 3: Drowsy but responding to commands; 4: Asleep but responding to glabellar tap; 5: Asleep but sluggish response to touch; and 6: Asleep without any response to stimulus).

Patients were monitored for any side effects (discomfort, nausea, vomiting, shivering, bradycardia, and hypotension). Hypotension was defined as a drop in the MAP to 20% or more of the baseline value or systolic blood pressure of 90 mmHg or less and treated with a fluid bolus of lactated Ringer’s solution and incremental doses of intravenous mephenetamine 3.0 mg as appropriate. Heart rate of 50 beats/min or less was defined as bradycardia and was treated with intravenous atropine 0.6 mg. Respiratory rate of 9 breaths/min was defined to be respiratory depression.

Diclofenac 75 mg intramuscular was administered when patient complained of pain and the time noted. Its duration from spinal block was defined as postoperative analgesia duration.

Statistical Analysis: Sample size was calculated by considering the mean and standard deviation (SD) of pilot study for 10 cases of each group, at 80% power and 5% level of significance. Maximum sample size estimated by 2 independent sample mean for analysis was 25. The data were analysed using SPSS Version 20.0 (IBM, India). Parametric testing was done using one-way analysis of variance (ANOVA), intergroup comparison was done with post hoc analysis Tukey’s test and categorical data were analyzed using the Chi-square test. Data were presented as mean ± standard deviation (SD). The values of $P < 0.05$ were considered statistically significant.

**Results**

The demographic data, ASA grade, surgical type and duration were comparable between the two groups [Table 1].

| Table 1: Distribution of subjects according to demographic profile vital signs and Surgical characteristics |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Placebo (n=25)  | Clonidine (n=25) | Dexmedetomidine (n=25) | $p$ value |
| Age (yrs)       | 34.20±12.42     | 38.72±13.81     | 42.20±13.14     | 0.104         |
| Sex (M:F)       | 11:14           | 14:11           | 11:14           | 0.736         |
| Weight (kg)     | 62.88±7.468     | 62.80±8.534     | 59.72±5.962     | 0.234         |
| Height (cm)     | 163.76±7.149    | 160.96±7.260    | 160.96±6.275    | 0.261         |
| Baseline HR/min | 78.04±8.66      | 77.28±9.03      | 78.72±9.09      | 0.850         |
| Baseline MAP (mm Hg) | 95.08±6.48  | 96.28±4.73      | 93.80±4.564     | 0.265         |
| Surgical duration (min) | 117.72±8.541663 | 117.72±8.829496 | 116.64±9.077812 | 0.883         |

Values (except sex distribution) are Mean ± Standard Deviation.

The duration of sensory regression to S1 dermatome was significantly prolonged by dexmedetomidine (231.20±24.84 min) and clonidine (200±23.67 min) with respect to placebo (171±12.25 min) ($p < 0.001$). The motor block lasted 135.20±12.87 mins with placebo, 180.40 ± 24.70 min with clonidine and 205.20±25.56 min with dexmedetomidine. Both drugs prolonged it significantly ($p < 0.001$). Dexmedetomidine (255±23.14 min) provided a significantly prolonged postoperative analgesia when compared with clonidine (221.40±24.30 min) and placebo (202.60±14.08 min) ($p < 0.001$) [Table 2].

| Table 2: Duration of motor block, sensory block and analgesia |

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Clonidine</th>
<th>Dexmedetomidine</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of motor block</td>
<td>135.20 ± 12.87</td>
<td>180.40 ± 24.70</td>
<td>205.20 ± 25.56</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Duration of sensory block</td>
<td>171±12.25</td>
<td>200+23.67</td>
<td>231.20 ± 24.84</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Time to first request of</td>
<td>202.60±14.08</td>
<td>221.40±24.30</td>
<td>255 ± 23.14</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>postoperative analgesic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are in minutes, * statistically significant.

Though the mean heart rate (HR) remained lower with intravenous dexmedetomidine, the difference among the groups was not significant, except at 45 mins from the spinal anesthesia (p 0.036) [Fig. 1]. However, the drop was not clinically significant and therefore did not require any intervention.

![Fig. 1: Trend of Mean Heart Rate](image)

The mean sedation score was significantly higher in dexmedetomidine group at 30 and 45 min after spinal anesthesia. The MAP was significantly lower with both dexmedetomidine and clonodine, as compared to placebo. (p <0.001). However there was no hemodynamic instability as the mean MAP was always above 75 mm of Hg in all three groups [Fig. 2].

![Fig. 2: Trend of Mean Arterial Pressure](image)

The mean sedation score was significantly higher in dexmedetomidine group at 30 and 45 min after spinal anesthesia (p <0.001), as analysed by the Kruscal Wallis test. The Ramsay sedation score was more than 3 in 18 patients in the dexmedetomedine group as compared to 8 patients in clonidine group and 2 patients in placebo group.
The incidence of complications (bradycardia, hypotension or nausea and vomiting) was comparable between the groups [Table 3].

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Clonidine</th>
<th>Dexmedetomidine</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>0.471</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2</td>
<td>3</td>
<td>6</td>
<td>0.355</td>
</tr>
<tr>
<td>Ramsay sedation score &gt;3</td>
<td>2</td>
<td>8</td>
<td>18</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Nausea and Vomiting</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>0.999</td>
</tr>
</tbody>
</table>

Values are expressed as numbers, Fischer’s exact test used, * statistically significant

**Discussion**

Intravenous α2 agonists prolong the duration of subarachnoid block by their supra-spinal action at locus ceruleus and dorsal raphe nucleus. α2 receptors have three subtypes: α2A, α2 B and α2C. Activation of α2-A receptors, located presynaptically at locus ceruleus decrease the release of norepinephrine and leads to sedation and hypnosis, while those in the descending medullo-spinal noradrenergic pathway terminate the propagation of pain signals to provide analgesia. α2-A receptors at substantia gelatinosa in the spinal cord exhibit their analgesic action by inhibition of nociceptive neurons and hence preventing substance P release. Hypotension and bradycardia are attributed to post-synaptic α2-A receptor activation in CNS which in turn decreases sympathetic outflow. Thus α2 agonists effectively modulate pain at various levels of the pain pathway, through supraspinal, spinal and peripheral mechanisms. Dexmedetomidine is 8 to 10 times more selective at the α2-A receptors as compared to clonidine, and therefore has greater sedative and analgesic effects.8-11

In a systematic review and meta-analysis of various studies on facilitatory effects of intravenous dexmedetomidine on subarachnoid block, the dexmedetomidine dosage ranged from 1 to 4 mcg/kg over 10 to 20 minutes with or without a maintenance infusion.12 The drug was given either before, just after or 20 min after spinal anaesthesia. Though the dose equivalence of clonidine and dexmedetomidine has not yet been conclusively established; studies indicate that the required dose of clonidine should be around 1.5–2 times that of dexmedetomidine.3,9,10 We therefore used dexmedetomidine 1 mcg/ kg and clonidine 2 mcg/kg over 20minutes each. As the infusion was started 20 min after the spinal anaesthesia, we did not compare the effect of these drugs on the onset of sensorimotor block and also the highest level of block achieved.

In the present study, both the drugs prolonged the sensory and motor block duration significantly. Intergroup comparison showed significant prolongation of sensorimotor block by dexmedetomidine than clonidine, similar to Dinesh CN et al, Al Mustafa et al, Tekin et al, and Whizar-Lugo et al.11,13-15 However, study by Kaya et al did not demonstrate any significant prolongation of motor block by dexmedetomidine, while Reddy et al reported no prolongation with either clonidine or dexmedetomidine.16,17 The duration to the first demand of systemic analgesic was significantly prolonged by both drugs in our study and also previous studies.11-17 Intravenous clonidine and dexmedetomidine act at the locus ceruleus(supraspinal level)and prolong the subarachnoid block.11 The analgesic effects of α2-adrenergic agonists are attributed to their supraspinal, spinal, and peripheral sites of action.11,13 The mechanism of prolongation of motor block is unclear, although clonidine has been shown to directly inhibit the impulse conduction in Aα fibres (large, myelinated nerve fibres).18 Similar mechanisms may be attributed to dexmedetomidine.13,17 Dexmedetomidine being a more selective alpha 2A-adrenoceptor agonist than clonidine has a greater sedative and analgesic effect than the latter.14

Hemodynamic parameters remained stable intraoperatively and postoperatively. Though the incidence of hypotension and bradycardia was greater with dexmedetomidine, they were not clinically significant and did not require any treatment. These hemodynamic changes are attributed to decrease in the central sympathetic outflow by the synergistic effect of alpha 2-adrenoceptor agonists and spinal anesthesia.

In our study, we observed excessive sedation in 18 patients receiving dexmedetomidine group, 8 patients receiving clonidine and 2 patients in the placebo group. This can be attributed to a selective action of dexmedetomidine at 2A subtype of alpha-adrenoceptor,14 Dexmedetomidine distinguishes form other class of sedatives in that the patients receiving dexmedetomodine are easily arousable and stay cooperative which is a definite advantage, especially when used along with regional anaesthesia.19 Also, in our study we did not encounter respiratory depression, which is in concordance with the previous studies.12 The limitation of our study is a relatively smaller size of study population, it nonetheless had significant results.

**Conclusion**

Single dose intravenous dexmedetomidine and clonidine when administered after subarachnoid anesthesia with bupivacaine, prolong the duration of the sensory block, motor block as well as postoperative analgesia, without any significant side effects.
Dexmedetomidine is a comparably more effective adjuvant than clonidine.

References