Intravenous dexmedetomidine versus clonidine for prolongation of bupivacaine spinal anesthesia and analgesia: A randomized double-blind study

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Abstract

Background: Alpha2-adrenergic agonists have synergistic action with local anesthetics and may prolong the duration of sensory, motor blockade and postoperative analgesia obtained with spinal anesthesia.

Aim: The objectives of this study are to compare and evaluate the efficacy of intravenous dexmedetomidine premedication with clonidine and placebo on spinal blockade duration, postoperative analgesia and sedation in patients undergoing surgery under bupivacaine intrathecal block.

Materials and Methods: In this prospective, randomized, double-blind placebo-controlled study, 75 patients of the American Society of Anesthesiologists status I or II, scheduled for orthopedic lower limb surgery under spinal anesthesia, were randomly allocated into three groups of 25 each. Group DE received dexmedetomidine 0.5 µgkg⁻¹ and placebo group PL received 10 ml of normal saline intravenously before subarachnoid anesthesia with 15 mg of 0.5% hyperbaric bupivacaine. Onset time and regression times of sensory and motor blockade, the maximum upper level of sensory blockade were recorded. Duration of postoperative analgesia and sedation scores along with side effects were also recorded. Data was analyzed using analysis of variance or Chi-square test, and the value of \( P < 0.05 \) was considered statistically significant.

Results: The sensory block level was higher with dexmedetomidine (T4 ± 1) than clonidine (T6 ± 1) or placebo (T6 ± 2). Dexmedetomidine also increased the time (243.35 ± 56.82 min) to first postoperative analgesic request compared with clonidine (190.93 ± 42.38 min, \( P < 0.0001 \)) and placebo (140.75 ± 28.52 min, \( P < 0.0001 \)). The maximum Ramsay sedation score was greater in the dexmedetomidine group than other two groups (\( P < 0.0001 \)).

Conclusion: Premedication with intravenous dexmedetomidine is better than intravenous clonidine to provide intraoperative sedation and postoperative analgesia during bupivacaine spinal anesthesia.

Key words: Clonidine, dexmedetomidine, intravenous, postoperative analgesia, premedication

Introduction

Many techniques and drug regimens, with partial or greater success, have been tried from time to time to eliminate the anxiety component and to prolong the postoperative analgesia during regional anesthesia.\(^{[1,2]}\) Alpha2-adrenergic agonists have both analgesic and sedative properties, when used as an adjuvant to regional anesthesia.\(^{[3,4]}\) They potentiate the effect of local anesthetics and prolong the duration of both motor, sensory spinal blockade and postoperative analgesia.\(^{[5,7]}\) Clonidine is a partial \( \alpha_2 \)-adrenoreceptor agonist used intrathecally, with a well-established record of efficacy and safety.\(^{[6]}\)

Dexmedetomidine is a selective \( \alpha_2 \)-adrenoreceptor agonist; it has a \( \alpha_2/\alpha_1 \) selectivity ratio which is eight to 10 times higher than that of clonidine.\(^{[6]}\) Analgesic and sedative properties were found when intrathecal, epidural or intravenous dexmedetomidine was used as an adjuvant in previous studies.\(^{[9,14]}\) There is paucity of studies which have compared the dose equivalence of these two drugs, however various studies have established that the dose of clonidine is 1.5-2 times higher than the dose of dexmedetomidine.\(^{[15-18]}\)
We designed a prospective, randomized, double-blind, placebo-controlled clinical study, to evaluate and compare the efficacy of intravenous dexmedetomidine with clonidine and placebo on spinal blockade duration, postoperative analgesia and sedation as premedication to intrathecal bupivacaine.

**Materials and Methods**

After approval of the study protocol by our institutional ethics committee, written informed consent was obtained from each patient. Seventy-five ASA status I and II patients, of either sex, aged 40-60 years, weighing 50-70 kgs, measuring 150-170 cm height, with 20-25 kg/m² of body mass index (BMI), undergoing orthopedic lower limb surgery under spinal anesthesia were enrolled in the present study. Patients with a history of alcohol or drug abuse, diabetes mellitus, cardiac disease, hypertension, chronic obstructive respiratory disease, psychological disease, hepatic and/or renal disease, spinal deformities or any contraindication to spinal anesthesia (e.g., coagulation defects, infection at the puncture site, pre-existing neurological deficits in the body, etc.) and patients allergic to amide type of local anesthetics were excluded from the study.

On arrival to the operation theater, following insertion of an 18-G venous cannula, all patients received 500 ml of Ringer’s lactate solution before spinal anesthesia. Standard monitors like electrocardiography (ECG), non-invasive blood pressure (NIBP) and pulse oximetry (SpO₂) were attached and the baseline parameters were recorded. Using a computer-generated randomization schedule, the patients were randomly divided into three groups, group DE (n = 25) received dexmedetomidine 0.5 µgkg⁻¹; group CL (n = 25) received clonidine 1.0 µgkg⁻¹; and group PL (placebo, n = 25) received 10 ml of physiological saline, before spinal anesthesia. The study drugs were premixed to a total volume of 10 ml and were administered intravenously over a period of 10 min as a single dose by an anesthesiologist not involved in the study. Five minutes after the end of the infusion, with the patients in the sitting position, lumbar puncture was performed at L₃-L₄ spinal interspace through a standard midline approach using a 25-G Quincke spinal needle. Hyperbaric, 0.5% bupivacaine 15 mg was injected intrathecally, and all patients received oxygen 5 Lmin⁻¹ via a face mask throughout the procedure after approximating them to the surgical position. The patient and the anesthesiologist were blinded to the treatment group, and all recordings were performed by an anesthesiologist blinded to group allocation. Sensory blockade was assessed using sterile pin prick method in the mid-axillary line on both sides of chest. Immediately after sensory block assessment, motor block was assessed using a modified Bromage scale²⁰ (grade 0: No paralysis; 1: Unable to raise extended leg; 2: Unable to flex knee; 3: Unable to flex ankle).

Sensory and motor block was assessed every minute for the first 10 minutes (mins) and thereafter every 10 mins during surgery and every 15 mins, postoperatively. Onset times of both sensory and motor blockade were assessed and recorded. The highest dermatomal level of sensory blockade and recovery times of both sensory and motor blockade was recorded. Recovery time for the sensory blockade was defined as two-dermatome regression of anesthesia from the maximum level. Motor block duration was the time to return to grade-1 on the modified Bromage scale. Postoperative pain was assessed by using the visual analog scale,²⁰ (VAS; 0: No pain; 10: Worst possible pain) at 4, 8, 12 and 24 hr. Patients with a VAS score of 3 or more received injection Diclofenac sodium 75-mg intramuscularly. The time of first request for postoperative analgesia after surgery was recorded as duration of postoperative analgesia.

The Ramsay sedation score, was used to assess sedation (1: Anxious or agitated; 2: Co-operative and tranquil; 3: Drowsy but responsive to command; 4: Asleep but responsive to glabellar tap; 5: Asleep with a sluggish response to tactile stimulation; and 6: Asleep and no response). The score was re-evaluated every 10 min after administration of drug for up to 180 min and every 15 min thereafter. Excessive sedation was defined as a sedation score which was greater than four (5/6).

The anesthesiologist who performed the block recorded the vital data, heart rate (HR), mean arterial pressure (MAP), oxygen saturation (SpO₂), respiratory rate (RR) before premedication, 2 min after end of premedication, immediately before and 60 seconds after dural puncture, every 5 min after spinal anesthesia during surgery and every 15 minutes in the postoperative ward until a complete reversal of spinal block. Hypotension (defined by a decrease in MAP below 20% of baseline or systolic pressure <90 mmHg) was treated with incremental doses of mephentermine 3.0 mg i.v., and additional lactated Ringer’s solution as appropriate. Bradycardia (HR < 50 beats/min) was treated with atropine 0.5 mg i.v., to avoid masking of respiratory depression by administering supplemental oxygen, respiratory depression was defined as a respiratory rate <12 breaths min⁻¹.

**Statistical analysis**

Sample size calculation was based on a previous study,¹⁵ for which we assumed a standard deviation (SD) of 24 min in time to sensory regression of two dermatomes, an α-error of 0.05, and a β-error of 0.2. To show a 20% difference in sensory regression of two dermatomes, at least 23 patients per group were needed, so we selected 25 patients per group. The data were analyzed statistically using Graph Pad prism 5.02 version, parametric testing was done using one-way analysis of variance (ANOVA), intergroup comparison was
done with Tukey-Kramer multiple comparison (TKMC) test and categorical data were analyzed using the Chi-square test. Data was presented as mean ± SD or number of patients (percentage) per category. The values of $P < 0.05$ were considered to indicate statistical significance.

**Results**

Spinal anesthesia was successful in all the patients and all the 75 patients completed the study. The demographic profiles of the patients among the groups were comparable with regards to age, weight and body mass index. The distribution of vital data and mean duration of surgery was comparable among the groups [Table 1].

Intravenous dexmedetomidine premedication during bupivacaine spinal anesthesia resulted in early onset of sensory block to T10 level (2.91 ± 1.16 min) as compared to clonidine (3.58 ± 0.6 min) and achieved maximum upper level of sensory block (T4 ± 1) which is higher than clonidine (T6 ± 1) or placebo (T6 ± 2). Time of onset of motor block was reduced by dexmedetomidine (3.64 ± 0.75 min) but not by clonidine (4.21 ± 1.49 min) when compared with placebo (4.57 ± 0.83 min). Time for sensory regression of two dermatomes was 148.54 ± 20.66 mins in the dexmedetomidine group which was longer than the clonidine (126.38 ± 16.04 min) or the placebo (95.38 ± 17.41 min) groups. Dexmedetomidine also increased the time to first request for postoperative analgesia (243.35 ± 56.82 min) compared with clonidine (190.93 ± 42.38 min) and placebo (140.75 ± 28.52 min). Duration of motor block was not significantly prolonged by either of the drugs [Table 2].

When we observed the trend of mean HR [Figure 1], heart rates in the dexmedetomidine group appears to be lower than that of clonidine and placebo groups, but there is no statistically significant difference among the groups except at 5 mins after spinal anesthesia where the mean heart rate was significantly lower ($P = 0.0299$). Mean heart rates of both the groups were above 70/min indicating the hemodynamic stability in dexmedetomidine and clonidine groups at given doses.

The trend of MAP [Figure 2], in our observation showed no significant difference in MAP among the groups before administration of premedication but both dexmedetomidine and clonidine group had a significantly lower MAP after premedication, up to 5 mins after spinal anesthesia when compared to saline group (ANOVA values of $P$: After premedication $P = 0.0347$, before spinal $P = 0.0055$, 2 mins after spinal $P = 0.0292$ and 5 minutes after spinal $P = 0.0418$). Dexmedetomidine and clonidine group do not differ significantly after premedication but after 2 mins and 5 mins of administration of spinal anesthesia, MAP was lower in the dexmedetomidine group ($P < 0.05$ by TKMC-test). Perioperative MAP was above 75 mm of Hg among the

### Table 1: Patient’s characteristics and preoperative vital data

| Variables                  | Group PL (n=25) | Group CL (n=25) | Group DE (n=25) | Value of P |
|----------------------------|----------------|----------------|----------------|------------|
| Age (years)                | 48.81±7.16     | 47.23±6.84     | 47.7±6.93      | 0.7144     |
| Weight (Kg)                | 55.47±5.72     | 56.2±5.49      | 56.7±6.23      | 0.7517     |
| Height (Cm)                | 161.51±8.7     | 161.83±7.41    | 160.65±6.92    | 0.8554     |
| BMI (Kg/m²)                | 21.14±1.87     | 21.42±1.52     | 21.87±2.13     | 0.3790     |
| Sex (Male:Female)          | 9:16           | 8:17           | 9:16           | -          |
| Baseline RR (breaths/min)  | 17.14±1.82     | 16.37±1.32     | 16.48±1.47     | 0.1722     |
| Baseline HR (beats/min)    | 77.67±11.88    | 80.57±13.2     | 81.13±13.58    | 0.5982     |
| Baseline MAP (mmHg)        | 97.33±10.6     | 96.53±16.71    | 100.64±12.98   | 0.5324     |
| Duration of surgery (min)  | 104.35±25.71   | 114.66±18.9    | 106.72±29.21   | 0.3166     |

*Values are mean±SD, and numbers; One-way ANOVA with Tukey-Kramer multiple Comparisons test, BMI=Body mass index, RR=Respiratory rate, HR=Heart rate, MAP=Mean arterial pressure, mm of Hg=Millimeters of mercury, min=Minutes, PL=Placebo, CL=Clonidine, DE=Dexmedetomidine

### Table 2: Highest sensory level, sensory and motor regression times and postoperative analgesia

| Variables                  | Group PL | Group CL | Group DE | Value of P |
|----------------------------|----------|----------|----------|------------|
| Time of onset of sensory block (min) | 4.26±1.37 | 3.58±1.06 | 2.91±1.16* | 0.0008*    |
| Time of onset of motor block (min)   | 4.57±0.83 | 4.21±1.49 | 3.64±0.75* | 0.0168*    |
| Highest sensory level (segments)     | T5-T8    | T4-T6    | T3-T5    | -          |
| Time for two-segment regression of sensory block (min) | 95.38±17.41 | 126.38±16.04 | 148.54±20.66 | <0.0001*   |
| Time for regression of motor block to Bromage grade-1(min) | 139.89±32.18 | 150.47±18.66 | 146.53±31.62 | 0.4112     |
| Time of first request of analgesic (min) | 140.75±28.52 | 190.93±42.38 | 243.35±56.82 | <0.0001*   |

*Values are mean±SD, and numbers. PL=Placebo, CL=Clonidine, DE=Dexmedetomidine, *Differ significantly. One-way ANOVA with Tukey-Kramer multiple comparisons test done
groups, at all times, indicating the hemodynamic stability in dexmedetomidine and clonidine groups at given doses.

Mean sedation scores were significantly higher in the dexmedetomidine group (P < 0.0001). Patients with sedation scores greater than three were 68% in dexmedetomidine group, 24% in clonidine group and 12% in the placebo group. Bradycardia, hypotension, nausea and vomiting were not statistically significant among the groups [Table 3].

**Discussion**

Dexmedetomidine and clonidine, have been used as adjuvants to local anesthetics by intrathecal, epidural, caudal, intravenous routes and for peripheral nerve blocks. Dexmedetomidine is a highly selective \( \alpha_2 \)-adrenoreceptor agonist with \( \alpha_2: \alpha_1 \) binding ratio of 1620:1 compared to 220:1 for clonidine.[20,21]

Dexmedetomidine has been used intravenously in doses ranging from 0.1 to 10 \( \mu \)g/kg/h but higher doses have been associated with a significant incidence of bradycardia and hypotension.[22,23] Aantaa et al.,[24] concluded that “The optimal dose of dexmedetomidine for single dose intravenous premedication in minor surgery appears to be in the range of 0.33 to 0.67 \( \mu \)g/kg. Jaakolaet al.,[25] demonstrated moderate analgesia with a ceiling effect at a dose of 0.5 \( \mu \)gkg\(^{-1} \). Thus we selected a dose of 0.5 \( \mu \)gkg\(^{-1} \) as premedication in our study. As rapid administration of dexmedetomidine might produce tachycardia, bradycardia and hypertension,[26] we administered dexmedetomidine, 0.5 \( \mu \)gkg\(^{-1} \) slowly, over a period of 10 min in our study. Previous studies have elucidated a dose of clonidine, which is 1.5-2 times higher than the dose of dexmedetomidine.[15,27] Based on the observations of previous studies[15,26] a dose of 1.0 \( \mu \)gkg\(^{-1} \) of clonidine was selected in our study.

In our study, both dexmedetomidine and clonidine reduced the onset times of sensory and motor block, and prolonged the duration of sensory blockade. However the duration of motor blockade was not prolonged. Similar results have been observed by Fatma Nur Kaya et al. The analgesia produced by \( \alpha_2 \)-agonist is due to their action at spinal, supra-spinal, direct analgesic and/or vasoconstricting actions on blood vessels.[29] The locus ceruleus and the dorsal raphe nucleus are the important central neural structures where these drugs act to produce sedation and analgesia.[22] This supra-spinal action could explain the prolongation of spinal anesthesia after intravenous administration of dexmedetomidine and clonidine.

In our study, two-segment regression time of sensory block and time of first request for analgesic were significantly prolonged in the dexmedetomidine group than clonidine and placebo groups. This could be attributed to the mechanism of action of dexmedetomidine which differs from clonidine in being eight to ten times more selective to \( \alpha_2 \)-adrenoceptors especially for \( \alpha_2A \) and \( \alpha_2C \) subtype of this receptor.[22] Time for regression of motor block did not differ among the groups. The mechanism of motor block produced by \( \alpha_2 \)-agonist is unclear but there is some evidence that clonidine results in direct inhibition of impulse conduction in the large, myelinated A-\( \alpha \) fibers. The 50% effective concentration (EC50%) measured to block motor fibers is approximately 4-folds that of small,

| Variables          | Group PL | Group CL | Group DE | P value |
|--------------------|----------|----------|----------|---------|
| Bradycardia        | 2        | 2        | 5        | 0.3210  |
| Hypotension        | 1        | 3        | 5        | 0.2198  |
| Sedation score (>3)| 3        | 6        | 17       | <0.0001*|
| Nausea and vomiting| 2        | 3        | 1        | 0.5807  |

Values are numbers, Chi-squared test was done, PL=Placebo, CL=Clonidine, DE=Dexmedetomidine, *Statistically significant

**Figure 1:** Comparison of heart rate in the PL, DE and CL groups, covering the pre-, intra- and post-operative period

**Figure 2:** Comparison of mean arterial pressure (MAP) in the group PL, DE and CL covering the pre-, intra- and post-operative period
unmyelinated C fibers.\textsuperscript{30} This could explain the less prolonged motor block compared with sensory block, as conduction of motor nerve fibers were less inhibited than sensory nerve fibers at the same concentration of clonidine. A similar mechanism can explain the prolongation of sensory block as compared with the motor block in the dexmedetomidine group.

Hemodynamic parameters, both HR and MAP were stable during perioperative period and the fall in HR and MAP were less than 20% from baseline among the groups. The incidence of hypotension and bradycardia were more in the dexmedetomidine group but not statistically significant. These hemodynamic changes were due to decrease in central sympathetic outflow.

The sedation produced by dexmedetomidine differs from other sedatives, as patients may be easily aroused and remain co-operative.\textsuperscript{31} In our study, excessive sedation was observed in two patients of the dexmedetomidine group compared with no patient in the clonidine and placebo group. Studies report minimal to none respiratory depression following dexmedetomidine administration,\textsuperscript{32} which has also been validated by the results of our study.

**Conclusions**

Single dose of intravenous dexmedetomidine resulted in an early onset action of bupivacaine, rapid establishment of both sensory and motor blockade, prolonged duration of analgesia into the postoperative period and stable cardiovascular parameters thereby making dexmedetomidine an effective adjuvant than clonidine for bupivacaine spinal anesthesia.

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