

Comparison of Block Characteristics and Hemodynamic Effects of Low Doses of Clonidine and Dexmedetomidine as an Adjuvant to Hyperbaric Bupivacaine for Spinal Anesthesia in Patients Undergoing Lower-limb Surgeries

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Abstract

Background: Various adjuvants are being used with local anesthetics for prolongation of intraoperative and post-operative analgesia. Among them, clonidine and dexmedetomidine are two α_2 -agonists which can be used as neuraxial adjuvants. Dexmedetomidine, a highly selective α_2 -adrenergic agonist, is a newer neuraxial adjuvant gaining popularity.

Objectives: The objective of the study was to compare sensory and motor block characteristics, hemodynamic effects and side effects of low doses of clonidine or dexmedetomidine as an adjuvant to 12.5 mg hyperbaric bupivacaine in spinal anesthesia in lower-limb surgeries.

Materials and Methods: A total of 90 patients of American Society of Anesthesiology I and II posted for lower-limb surgeries were randomly allocated into three groups of 30 each. Group B received plain 12.5 mg of hyperbaric bupivacaine diluted to 3 ml with normal saline. Group C received 30 mcg clonidine added to 12.5 mg hyperbaric bupivacaine and diluted to 3 ml. Group D received 3 mcg dexmedetomidine added to 12.5 mg hyperbaric bupivacaine and diluted to 3 ml with normal saline.

Results: Patients in Group D and Group C had a significantly shorter onset time of sensory and motor block and significantly longer duration of sensory and motor block compared to bupivacaine group. The mean time for sensory regression to S1 segment was 301.90 ± 31.96 min in Group D, 283.23 ± 13.59 min in Group C, and 181.70 ± 18.55 min in Group B (B vs. D and B vs. C, $P < 0.001$). There was a statistically significant difference in the two segment regression of sensory block in Group D (140.32 ± 17.6 min) when compared to Group C (124.5 ± 16.10 min) and Group B (92.13 ± 11.45 min). The regression of motor block to Bromage 0 was 262 ± 24.40 min in Group D, 261 ± 24.19 min in Group C, and 164.40 ± 15.26 min in Group B (B vs. D and B vs. C, $P < 0.0001$). The onset and regression times were comparable between Groups D and C. Time for the first request of rescue analgesia was nearly equal in Groups D and C and prolonged compared to Group B. Patients were hemodynamically stable in all the groups.

Conclusion: Dexmedetomidine and clonidine have a similar onset of sensory and motor block, prolonged duration of analgesia. Dexmedetomidine provides better analgesia than clonidine.

Key words: Adjuvants, Alpha 2- adrenergic agonists, Clonidine, Dexmedetomidine, Hyperbaric Bupivacaine, Intrathecal

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INTRODUCTION

The subarachnoid blockade is the most commonly used regional anesthetic technique for lower-limb surgeries. It offers the advantage of prolonged anesthesia with fewer side effects compared to general anesthesia. It is easy to perform and provides faster onset and effective

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sensory and motor blockade.^[1] Bupivacaine is the local anesthetic drug commonly used in spinal anesthesia without significant neurological symptoms.^[2] The routine doses of bupivacaine produce significant sympathetic block which may not be desirable in some patients. Addition of adjuvants^[3] to spinal local anesthetics decreases the incidence of side effects of local anesthetics and increases the duration of sensory and motor blockade.^[4] Many adjuvants are used in spinal anesthesia, which includes opioids, epinephrine,^[5] magnesium sulfate,^[6] and α -2 adrenergic agonists. Alpha-2 adrenergic agonists have been demonstrated to have sedative, analgesic, perioperative sympatholytic, anesthetic sparing, and hemodynamic stabilizing properties.^[7] α_2 - adrenergic agonists have the ability to potentiate the effects of local anesthetics.^[8] Unlike spinal opioids, α_2 -agonists do not produce pruritis and respiratory depression.^[9] At present, two major α_2 -agonists used in perioperative care are clonidine and dexmedetomidine.^[10]

Clonidine is the first clinically used α_2 -adrenergic agonist, with a well-established record of safety and efficacy.^[11] Preservative-free clonidine, when administered into subarachnoid space, shares similar analgesic pathways to local anesthetics and has been shown to interact synergistically with local anesthetics.^[11] Dexmedetomidine is an S-enantiomer of medetomidine with a higher specificity for α_2 -adrenoceptor ($\alpha_2:\alpha_1$, 1620:1) compared to clonidine ($\alpha_2:\alpha_1$, 220:1).^[12,13] It was first introduced into the practical use as an intravenous sedative agent in mechanically ventilated patients in the intensive care unit after the approval of United States Food and Drug Administration in 1999.^[12] Since then it has been investigated as an anxiolytic, sympatholytic and analgesic properties related to α_2 -adrenoceptor binding.^[12,13] As a neuraxial adjuvant, dexmedetomidine's high lipophilicity facilitates rapid absorption into the cerebrospinal fluid and binding to the spinal cord α_2 -adrenoceptors. In view of limited studies about the efficacy of dexmedetomidine as an adjuvant in spinal anesthesia, we planned a double-blinded randomized controlled study to compare the spinal block characteristics and side effects along with hemodynamic changes following intrathecal bupivacaine versus intrathecal bupivacaine supplemented with a low dose of either clonidine or dexmedetomidine in patients scheduled for lower-limb surgeries.

MATERIALS AND METHODS

After obtaining approval from the Hospital Ethics Committee, 90 adult patients of either sex in the age group 18–50 years, belonging to American Society of Anesthesiology Class I and II and scheduled for elective

lower limb surgery under subarachnoid block, were enrolled in this prospective, randomized, and double-blinded study. Patients with contraindication to regional anesthesia, history of significant coexisting diseases such as ischemic heart disease, hypertension, impaired renal functions, rheumatoid arthritis, and severe liver disease were excluded from the study. Patients on adrenergic agonist and antagonist therapy, pregnant patients, chronic alcoholics and malnourished patients, patients allergic to local anesthetic agents, and patients with psychiatric illness are also excluded from the study. Patients are allocated into three groups (Group B, Group C, and Group D) using a computer-generated randomization number table. After a thorough pre-operative assessment, patients who satisfied the inclusion criteria were explained about the nature of the study and the anesthetic procedure. Informed written consent was obtained from all the patients included in the study. Sedatives and hypnotics were avoided in pre-operative and intraoperative period. Patients were premedicated with ondansetron (4 mg IV). In the operating room, patients were preloaded with Ringer Lactate solution 10–15 ml/kg. Baseline hemodynamic parameters heart rate (HR), oxygen saturation (SpO_2), and mean blood pressure (BP) were noted. Under strict aseptic precautions, subarachnoid block was performed in a sitting position through the midline approach, using a 25G Quincke needle and study drug solution (3 ml) injected. Spinal anesthetic preparations were done as follows: Group B: Inj. Bupivacaine 0.5% 12.5 mg (2.5 ml) + normal saline 0.5 ml, Group C: Inj. Bupivacaine 0.5% 12.5 mg + injection Clonidine 30 μ g + 0.3 ml normal saline, and Group D: Inj. Bupivacaine 0.5% 12.5 mg + injection Dexmedetomidine 3 μ g + 0.2 ml normal saline. The patients were placed in supine position after injection of the study drug, and the sensory level was assessed by pinprick sensation along the mid-clavicular line bilaterally every 3-min for 30 min and then every 15 min afterward. The time to reach T10 dermatome (onset time), the maximum sensory level achieved, and time for two segment and S1 segment regression (the total duration of the sensory block) were recorded. The motor block was assessed according to the modified Bromage scale (0–3), for onset (time to reach maximum Bromage level), and duration (time to Bromage 0 regression). Pulse rate, BP, respiratory rate, and SpO_2 were monitored every 3 min for the first 30 min and then every 15 min for 180 min. Any discomfort such as nausea, vomiting, dry mouth, and shivering was noted. Hypotension defined as fall in systolic BP (SBP) > 30% from baseline or mean arterial pressure < 60 mmHg and was treated with intravenous fluid bolus and Inj. Ephedrine 3 mg in incremental doses. Bradycardia (<50/min), if present was treated with Inj. Atropine 0.01 mg/kg intravenously. Sedation was assessed using the Ramsay Sedation Score and the pain was assessed using a Visual analog scale (VAS). Postoperatively in

the post-anesthesia care unit (PACU) pain scores and observations were made by the staff and data entered as per the instructions. Post-operative rescue analgesic was provided by injection Paracetamol 1 g I.V. and injection Tramadol 50 mg I.V. The anesthesiologist who made the drug combination took no further part in the study. A single observer performed the subarachnoid block and made intraoperative observations.

Statistical Analysis

The collected data were analyzed with IBM.SPSS statistics software 23.0 Version. To describe about the data, descriptive statistics frequency analysis and percentage analysis were used for categorical variables and the Mean \pm S.D was used for continuous variables. To find the significant difference in the multivariate analysis, the one-way analysis of variance (ANOVA) with Tukey's *Post hoc* test was used. To find the significance in categorical data Chi-square test was used. In both the above statistical tools, the probability value 0.05 is considered as significant level.

RESULTS

Confounding variables such as age, sex, height, weight, and duration of surgery were comparable in all the three groups, and there was no statistically significant difference between them. The mean time required to reach T10 sensory block level was 5.97 ± 0.94 min in Group B, 4.13 ± 0.93 min in Group C, and 3.99 ± 0.66 min in Group D, as shown in Table 1. Intergroup comparison B to C and B to D, $P < 0.05$ was significant whereas C to D was not significant > 0.05 . In respect to the motor blockade, all patients achieved Bromage three motor block. The time to reach Bromage scale three was 4.23 ± 1.33 min in Group B, 2.39 ± 0.7 min in Group C, and 2.32 ± 0.64 min in Group D. Intergroup comparison B to C and B to D was, $P < 0.0001$ was significant. It was fastest in Group D followed by Group C and last Group B. The time to reach Bromage scale 0 was 164.36 ± 15.26 min in Group B, 261.77 ± 24.19 min in Group C, and 262.33 ± 24.40 min in Group D. Intergroup comparison B to C and B to D, $P < 0.05$ was significant. It was longest in Group D followed by Group C and then Group B as shown in Table 2. The two segments regression time was 92.13 ± 11.45 min in Group B, 124.5 ± 16.10 min in Group C, and 140.32 ± 17.6 min in Group D. Intergroup comparison B to C, B to D, and C to D was significant

(< 0.05). It was longest in Group D followed by Groups C and B. The time to regression time to S1 dermatome was 181.7 ± 18.55 min in Group B, 283.23 ± 13.59 min in Group C, and 301.90 ± 31.96 min in Group D. Complete recovery of sensory function was observed in all studied patients. Intergroup comparison B to C, B to D, and C to D was significant ($P < 0.05$). The time of first rescue dose requested by the patient was 171.67 ± 17.15 min in Group B, 288 ± 31.93 min in Group C, and 287.07 ± 17.14 min in Group D. Intergroup comparison B to C and B to D was significant. Mean HR in Group B was 82.89 ± 6.40 , in Group C it was 67.49 ± 4.96 , and in Group D it was 60.49 ± 6.54 . Intergroup comparison among the three groups was statistically significant. Significant bradycardia (HR $< 50/\text{min}$) was observed in two patients in Group D. SBP was $106.92 \pm 7.58\text{mmhg}$ in Group B, $96.77 \pm 7.84\text{mmhg}$ in Group C, and $88.89 \pm 9.80\text{mmhg}$ in Group D. Mean diastolic BP (DBP) was $71.47 \pm 1.56\text{mmhg}$ in Group B, $63.61 \pm 2.47\text{mmhg}$ in Group C, and $60.85 \pm 1.35\text{mmhg}$ in Group D. Mean arterial BP was $84.50 \pm 3.33\text{mmhg}$ in Group B, $75.89 \pm .98\text{mmhg}$ in Group C, and $68.58 \pm 7.34\text{mmhg}$ in Group D. There is a significant difference among all the three groups as shown in Table 3. Hypotension is observed in all the groups during the initial 15 min of the subarachnoid block but the use of inj. Ephedrine is more in clonidine and dexmedetomidine group. There is no significant difference in view of the type of surgery and duration of surgery among all the groups. Mean visual analog score and Ramsay Sesation Scores among groups shown in Table 4.

DISCUSSION

Alleviation of acute and chronic pain has become a challenge to the anesthesiologist. The early success of pharmacologic endeavors in pain mitigation involved extensive use of opioids. Although reasonably successful, it was often associated with systemic complications such as nausea, vomiting, respiratory depression, sedation, delayed recovery of bowel functions, and hyperalgesia. In an effort to reduce the need and adverse effects of systemic opioids, the perineural (intrathecal, epidural, or peripheral nerve blocks) use of local anesthetics has gradually evolved over time.^[1] Although beneficial in acute and chronic pain management, local anesthetics do have the potential to produce deleterious effects such as

Table 1: Sensory block characteristics

Parameters	Group B	Group C	Group D
Mean onset of sensory block (min)	3.40 ± 1.52	1.76 ± 0.63	1.75 ± 0.78
Meantime to reach maximum sensory level	5.97 ± 0.94	4.13 ± 0.93	3.99 ± 0.66
Two segment regression of sensory block	92.13 ± 11.45	124.5 ± 16.10	140.32 ± 17.6
Time taken for regression to S1 dermatome (min)	181.7 ± 18.55	283.23 ± 13.59	301.90 ± 31.96

Table 2: Motor block characteristics

Parameters	Group B	Group C	Group D
Onset of motor block	4.23±1.33	2.39±0.7	2.32±0.64
Time to reach	164.36±15.26	261.77±24.19	262.33±24.40
Bromage score 0			

Table 3: Hemodynamic parameters

Parameters	Group B	Group C	Group D
Mean systolic BP	106.92±7.58	96.77±7.84	88.89±9.80
Mean DBP	71.47±1.569	63.619±2.48	60.857±1.35
MAP	84.5±3.336	75.89±4.98	68.58±7.34
HR	82.89±6.40	67.49±4.96	60.49±6.54

HR: Heart rate, BP: Blood pressure, MAP: Mean arterial pressure, DBP: Diastolic blood pressures

Table 4: Visual analog score and Ramsay Sedation Score

Parameters	Group B	Group C	Group D
Mean visual analogue score	3.13±0.82	2.49±0.74	1.86±0.32
Mean ramsay sedation score	1.362±0.1008	1.696±0.220	1.978±1.70

cardiac arrhythmias, central nervous system depression, seizures, respiratory depression, hypertension, and allergic reactions. By prolonging the duration of sensory and motor block and limiting the cumulative dose requirement of local anesthetics, coadministration of adjuvants has the potential to improve the efficacy of perineural blocks and decrease local anesthetic toxicity. They contribute in their own special manner to potentiate the analgesic effect of the local anesthetics.^[4]

Clonidine and dexmedetomidine are α -2 adrenergic receptor agonists. The analgesic effect following their intrathecal administration is mediated spinally through the activation of postsynaptic α_2 -adrenoreceptors in substantia gelatinosa of the spinal cord.^[10] They prolong the duration of sensory and motor blockade and improve the quality of spinal anesthesia through different mechanisms involving descending inhibitory pain pathways.

In our study mean duration of onset of sensory block was 3.40 ± 1.52 min in Group B, 1.76 ± 0.63 min in Group C, and 1.75 ± 0.78 min in Group D. Onset of sensory block was minimized with the addition of clonidine or dexmedetomidine. The maximum sensory level was attained at the T10 level in all the groups. Meantime to reach maximum sensory level was 5.97 ± 0.94 min in Group B, in Group C 4.13 ± 0.93 min, and in Group D 3.99 ± 0.66 min. There is statistical significance among all the groups, using ANOVA test as $P < 0.0005$. Using Post hoc test, Tukey honest significant difference (HSD),

there is a significant difference between Group B and Group C and also between Group B and Group D. There is no statistical difference between Group C and Group D as $P > 0.792$. The maximum time taken for two segment regression of sensory block was observed in Group D (140.32 ± 17.6 min), followed by Group C (124.5 ± 16.10 min) and in Group B (92.13 ± 11.45 min). This shows the prolonged duration of sensory block in Group D compared to Group C and Group B. Maximum time taken to reach S1 dermatome was observed in Group D 301.90 ± 31.96 min. The minimum time taken by Group B 181.70 ± 18.55 min, and in Group C it was 283.23 ± 13.59 min. Using ANOVA test, there is a significant difference among all the three groups as $P < 0.005$. Using Post hoc test, Tukey HSD, significant difference between Groups B and C and Groups B and D was observed. However, between Groups C and D, no significant difference was observed as $P > 0.22$.

Asano *et al.*^[14] showed that the potency of neuraxial administered alpha 2-adrenoreceptor agonists well correlates with their binding affinity to spinal alpha-2 receptors. As the binding affinity of dexmedetomidine is 10 times more than clonidine and the doses we used in our study are 3 μ g of dexmedetomidine and 30 μ g clonidine, they might be equipotent and produced similar results. Similar findings were observed in the studies of Kanazi *et al.*^[15] where the addition of clonidine or dexmedetomidine resulted in the faster onset of sensory block.

Meantime for the onset of motor block was 4.23 ± 1.33 min in Group B, 2.39 ± 0.70 min in Group C, and 2.32 ± 0.64 min in Group D. Significant difference among all the three groups is found using ANOVA test, but using Post hoc test, Tukey HSD, no statistical difference between Groups C and D as $P > 0.985$. Duration of motor block, in Group D it was 262.33 ± 24.40 min, Group C 261.77 ± 24.19 min, and Group B 164.36 ± 15.26 min. Mahendru *et al.*^[9] studied that addition of dexmedetomidine increased the duration of motor block to 273.3 ± 24.6 min, clonidine group had 198.7 ± 24.6 min, and bupivacaine group had 161.5 ± 19.8 min. No statistically significant difference between Groups C and D, $P > 0.625$ and both the groups are comparable to each other.

Mean duration of time for the first request of analgesia was 171.67 ± 17.14 min in Group B, 288 ± 31.93 min in Group C, and 287.07 ± 17.145 min in Group D. Injection Tramadol 50 mg I.V and injection Paracetamol 1 g I.V were used as rescue analgesia in PACU. Prakash *et al.*^[11] in their studies observed the higher mean duration of analgesia in clonidine group (clonidine added as 1 μ g/kg body weight to 12.5 mg 0.5% bupivacaine), i.e., 614 min compared to 223 min of the control group (12.5 mg plain

0.5% bupivacaine). In our study, no significant difference was found between Groups C and Group D, as the dose of clonidine we used was only 30 µg.

VAS scores are similar in all the three groups during first 1 h of surgery and after 1 h scores were lower in Group D and Group C than Group B, and the difference is statistically significant among three groups. Sedation scores were lower in the dexmedetomidine group compared to bupivacaine and clonidine group, and the difference between clonidine and dexmedetomidine group is not statistically significant. Bradycardia (HR<50/min) was observed in two patients in the dexmedetomidine group. No patients had HR<50/min in clonidine and bupivacaine group.

CONCLUSION

Our study showed that addition of low dose clonidine (30 mcg) or dexmedetomidine (3 mcg) to hyperbaric bupivacaine for subarachnoid block effectively decreased the onset time of sensory and motor blockade and prolonged the mean duration of sensory and motor blockade. With both adjuvants, hypotension and bradycardia were the major adverse effects which were managed with standard methods. Dexmedetomidine provides better analgesia than clonidine. No significant difference in sedation scores observed between dexmedetomidine and clonidine groups.

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