Original Research

COMPARISON OF DIFFERENT DOSES OF INTRATHECAL CLONIDINE AS AN ADJUVANT TO LEVOBUPIVACAINE IN PATIENTS UNDERGOING LOWER LIMB ORTHOPAEDIC SURGERY: A RANDOMIZED DOUBLE-BLIND STUDY

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ABSTRACT

Background: Intrathecal adjuvants are commonly used to improve the quality and duration of spinal anesthesia in lower limb orthopedic surgeries. Clonidine, an α2-adrenergic agonist, prolongs sensory and motor blockade and postoperative analgesia when combined with local anesthetics; however, the optimal intrathecal dose of clonidine with hyperbaric levobupivacaine remains uncertain.

Objectives: To evaluate and compare the effects of intrathecal clonidine (15 µg and 30 µg) as an adjuvant to 0.5% hyperbaric levobupivacaine in patients undergoing lower limb orthopedic surgeries.

Methods: This prospective, randomized, double-blind study included 99 ASA I–II patients undergoing elective lower limb orthopedic surgery under spinal anesthesia. Patients were randomly allocated into three groups (n=33 each): Group A received hyperbaric levobupivacaine with saline, Group B received levobupivacaine with clonidine 15 µg, and Group C received levobupivacaine with clonidine 30 µg. Sensory and motor block characteristics, duration of postoperative analgesia, hemodynamic parameters, postoperative Visual Analog Scale (VAS) scores, and adverse effects were evaluated and compared among the groups.

Results: The onset of sensory and motor blockade was significantly faster in the clonidine groups, particularly in Group C ($P < 0.001$). Time to attain maximum sensory and motor blockade was also significantly reduced in Group C. Duration of motor block and postoperative analgesia increased with increasing clonidine dose. Mean duration of analgesia was highest in Group C (360.76 ± 55.21 min), followed by Group B (300.68 ± 43.20 min) and Group A (255.80 ± 33.61 min) ($P < 0.001$). Postoperative VAS scores at 4 hours were significantly lower in Group C. Although intraoperative heart rate and blood pressure were lower in the clonidine groups, the changes remained clinically manageable.

Conclusion: Intrathecal clonidine with hyperbaric levobupivacaine improved block characteristics and prolonged postoperative analgesia in a dosedependent manner. Clonidine 30 µg provided longest analgesia but caused greater, clinically manageable hemodynamic effects.

Keywords: Clonidine, Levobupivacaine, Spinal Anesthesia, Analgesia, Postoperative, Orthopaedic Procedures.

INTRODUCTION

Spinal anesthesia is widely preferred for lower limb orthopedic surgeries because of its rapid onset, reliable sensory and motor blockade, favorable safety profile, and cost-effectiveness. The use of intrathecal adjuvants is a well-established strategy to improve. The quality and duration of spinal anesthesia.

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Several agents, including opioids, dexmedetomidine, clonidine, midazolam, and magnesium sulfate, have been evaluated for this purpose. [1–4]

Clonidine, a centrally acting α2-adrenergic agonist, produces analgesia by stimulating spinal α2 receptors and inhibiting the release of nociceptive neurotransmitters, thereby potentiating the effects of Local anesthetics. Intrathecal clonidine has been shown to prolong sensory and motor blockade, enhance postoperative analgesia, and reduce postoperative analgesic requirements. Its sedative properties may additionally improve patient comfort during surgery.

Despite these advantages, the optimal intrathecal dose of clonidine remains uncertain. Higher doses may provide prolonged analgesia and improved spinal blockade but are also associated with dose-dependent adverse effects such as hypotension, bradycardia, and sedation.[5] Therefore, identifying a dose that provides effective analgesia with minimal hemodynamic compromise remains clinically important.

Levobupivacaine, the S(-) enantiomer of bupivacaine, is a long-acting local anesthetic with lower cardiotoxicity and neurotoxicity compared with racemic bupivacaine. The combination of levobupivacaine with clonidine may provide prolonged and effective spinal anesthesia with an improved safety profile. However, limited studies have directly compared different doses of intrathecal clonidine as an adjuvant to levobupivacaine in lower limb orthopedic surgeries.

Therefore, the present study was undertaken to evaluate and compare the effects of intrathecal clonidine (15 µg and 30 µg) as an adjuvant to 15 mg of 0.5% hyperbaric levobupivacaine with levobupivacaine alone in patients undergoing lower limb orthopedic surgeries. The primary objective was to compare the duration of postoperative analgesia among the study groups. Secondary objectives included comparison of sensory and motor block characteristics, hemodynamic parameters, and adverse effects associated with intrathecal clonidine.

MATERIALS AND METHODS

Study Design and Setting

This prospective, randomized, double-blind study was conducted in accordance with the ethical principles of the Declaration of Helsinki between August 2023 and January 2025 in the Department of Anaesthesiology at a tertiary care teaching hospital after obtaining approval from the Institutional Ethics Committee (AIMS/IEC/2023/91 dated 10/7/2023).

Study Participants

After obtaining written informed consent, adult patients aged 18–65 years belonging to the American Society of Anesthesiologists (ASA) physical status I–II and scheduled for elective lower limb orthopedic surgery under spinal anesthesia were included.

Patients with contraindications to spinal anesthesia, known allergy to study drugs, body mass index (BMI) ≥30 kg/m², severe cardiovascular disease, or neurological disorders were excluded from the study.

Sample Size and Randomization

Sample size was estimated based on the primary outcome variable, namely duration of postoperative analgesia, using data from a previous similar study evaluating intrathecal clonidine as an adjuvant to local anesthetics.[6] Assuming a study power of 80% and α error of 0.05, the estimated sample size was calculated using comparison of mean duration of analgesia between study groups. Considering possible dropouts and to improve the statistical robustness of intergroup comparisons, 99 patients were enrolled and equally allocated into three groups of 33 patients eachusing a computer-generated randomization table. Allocation concealment was performed using serially numbered sealed opaque envelopes.

- **Group A:** 3 mL of 0.5% hyperbaric levobupivacaine + 0.5 mL normal saline (total volume 3.5 mL)
- **Group B:** 3 mL of 0.5% hyperbaric levobupivacaine + clonidine 15 µg (0.1 mL) + 0.4 mL normal saline (total volume 3.5 mL)
- **Group C:** 3 mL of 0.5% hyperbaric levobupivacaine + clonidine 30 µg (0.2 mL) + 0.3 mL normal saline (total volume 3.5 mL)

The total intrathecal volume was maintained at 3.5 mL in all groups. Study drugs were prepared by an anaesthesiologist not involved in patient management to ensure double blinding.

Procedure

A detailed preanesthetic evaluation was performed one day before surgery. Patients were kept nil per oral for 6 h and received oral alprazolam 0.5 mg and omeprazole 20 mg on the night before surgery. The Visual Analog Scale (VAS; 0–10) was explained to all patients.

In the operating room, baseline heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and oxygen saturation (SpO_2) were recorded. After securing intravenous access with an 18G cannula, patients were co-loaded with Ringer's lactate solution (10 mL/kg).

Under strict aseptic precautions, subarachnoid block was performed at the L3–L4 or L4-L5 interspace using a 25G Quincke spinal needle in the lateral position. After confirmation of free cerebrospinal fluid flow, the study drug was administered intrathecally. Supplemental oxygen was administered through a face mask at 5–6 L/min throughout the procedure.

Assessment Parameters

Sensory Block

Sensory block was assessed by pinprick method at 2, 4, 6, 8, 10, 15, and 20 min after administration of subarachnoid block. Sensory block onset was defined as the time from intrathecal drug administration to loss of pinprick sensation at the T10 dermatome. The maximum sensory block level achieved and the time required to attain the maximum sensory block level were also recorded.

Motor Block

Motor block was assessed in the non-operated limb using the Modified Bromage Scale at 2, 4, 6, 8, 10, 15, and 20 min after administration of subarachnoid block and subsequently at the time of first rescue

analgesia. The maximum motor blockade achieved within the first 20 min and the duration of motor block were recorded.

Hemodynamic Parameters

Heart rate and blood pressure were assessed every 2 min for the first 10 min, every 5 min until 30 min, every 15 min until 1 h, and every 30 min thereafter until completion of surgery.

Hypotension was defined as a fall in systolic blood pressure >20% from baseline or SBP <90 mmHg and was treated with intravenous fluids and mephentermine 6 mg IV as required. Bradycardia was defined as heart rate <50 beats/min and was treated with atropine 0.6 mg IV.

Adverse Effects

Adverse effects such as nausea/vomiting, dry mouth, and shivering were recorded during the intraoperative and postoperative periods. Sedation was assessed every 15 min using the University of Michigan Sedation Scale.

Postoperative Analgesia

Postoperative pain was assessed using the Visual Analog Scale (VAS) in the postoperative care unit every 30 min until the patient complained of pain. Duration of postoperative analgesia was defined as the time from intrathecal injection to first request for rescue analgesia (VAS >3). Intravenous tramadol 2 mg/kg was administered as rescue analgesic, which was considered the study endpoint.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) software version 25.0 (IBM Corp., Armonk, NY, USA). Quantitative variables were expressed as mean ± standard deviation, while qualitative variables were expressed as frequency and percentage.

Intergroup comparisons of continuous variables were performed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. Categorical variables were analyzed using Chi-square test or Fisher's exact test, as appropriate. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 99 patients were enrolled and equally allocated into three groups (n=33 each). Baseline demographic and clinical characteristics, including age, sex distribution, ASA physical status, and duration of surgery, were comparable among the groups, with no statistically significant differences (P > 0.05) as can be seen in Table 1.

Table 2 shows the characteristics of sensory and motor blockade among the study groups. The onset of sensory and motor block was significantly faster in the clonidine groups compared with the levobupivacaine-alone group, with the shortest onset observed in Group C (30 µg clonidine) (P < 0.001). Time to attain maximum sensory and motor blockade was also significantly reduced in Group C. Duration of motor block and time to first rescue analgesia increased progressively with increasing clonidine dose, with Group C demonstrating the longest duration of analgesia (P < 0.001).

Table 3 shows the comparison of intraoperative hemodynamic parameters among the study groups. Baseline heart rate and blood pressure parameters were comparable among the groups (P > 0.05). However, the clonidine groups demonstrated significantly lower intraoperative heart rate and blood pressure values compared with the levobupivacaine-alone group. Group C (30 µg clonidine) showed the lowest intraoperative heart rate, mean arterial pressure, systolic blood pressure, and diastolic blood pressure (P < 0.05). Post hoc Tukey analysis demonstrated significantly lower intraoperative heart rate and blood pressure values in Groups B and C compared with Group A, with the greatest reductions observed in Group C, indicating a dose-dependent hemodynamic effect of clonidine. Despite these reductions, the hemodynamic changes remained clinically manageable and responded to standard therapeutic measures.

Postoperative pain was assessed using the Visual Analog Scale (VAS) at predefined intervals up to 6 hours postoperatively or until administration of the first rescue analgesic as shown in Table 4.

Postoperative VAS scores were comparable among the groups during the early postoperative period (1 h and 2 h). However, at 4 hours postoperatively, Group C demonstrated significantly lower pain scores compared with Groups A and B (P < 0.001), indicating prolonged postoperative analgesia with higher-dose clonidine. At 6 hours, significant intergroup differences persisted (P = 0.048), reflecting differences in the timing of rescue analgesic requirement among the study groups.

Dry mouthwas seen in two patients in Group B and three patients in Group C.Mild sedation wasseen in one patient in Group B and two patients in Group C. Shivering was observed only intwo patients in Group A. However, the differences were not statistically significant. No patient experienced nausea or vomiting during the study period.

DISCUSSION

The present study evaluated the effects of intrathecal clonidine (15 µg and 30 µg) as an adjuvant to 0.5% hyperbaric levobupivacaine in patients undergoing lower limb orthopedic surgery. The findings demonstrated that intrathecal clonidine improved sensory and motor block characteristics and prolonged postoperative analgesia, with greater effects observed at the higher dose.

Baseline demographic variables, ASA physical status, and duration of surgery were comparable among the study groups, thereby ensuring homogeneity and minimizing potential confounding bias.

In the present study, addition of clonidine accelerated the onset of sensory and motor blockade and reduced the time required to attain maximum blockade. Group C (30 µg clonidine) demonstrated the fastest onset and earliest attainment of peak blockade. Post hoc analysis showed significant intergroup differences for all sensory and motor block parameters, suggesting a dose-related effect of clonidine. These findings are comparable to previous study reporting improved spinal block characteristics with intrathecal clonidine as an adjuvant to local anesthetics.[7]

The findings of the present study regarding the primary outcome, namely duration of postoperative analgesia, are in agreement with previous reports. The duration of postoperative analgesia and time to first rescue analgesia increased significantly in the clonidine groups, with Group C demonstrating the longest duration of analgesia. Post hoc analysis revealed significant differences between all three groups for duration of analgesia, further supporting the analgesic efficacy of intrathecal clonidine. A similar prolongation of analgesia was reported by Krishna et al., who observed mean analgesia durations of 251.72 ± 31.62 min in the levobupivacaine-alone group, 294.68 ± 43.35 min in the levobupivacaine with clonidine 15 µg group, and 355.76 ± 52.19 min in the levobupivacaine with clonidine 30 µg group, with statistically significant intergroup differences ($P < 0.001$).[6] Similar prolongation in time to rescue analgesia has also been reported in other studies evaluating intrathecal clonidine.[7,8]

Hemodynamic parameters remained relatively stable in all groups, although transient reductions in heart rate and blood pressure were observed in the clonidine groups during the intraoperative period. Group C demonstrated the greatest reduction in intraoperative hemodynamic parameters. Post hoc analysis showed significantly lower heart rate and blood pressure values in Groups B and C compared with Group A, suggesting dose-related sympatholytic effects of clonidine. However, these changes were clinically manageable with standard therapeutic measures. Similar findings have been reported in previous study.[9-11]

Postoperative VAS scores were comparable among the groups during the early postoperative period. However, at 4 hours postoperatively, Group C demonstrated significantly lower pain scores compared with Groups A and B, indicating prolonged postoperative analgesia with higher-dose clonidine. Although significant intergroup differences persisted at 6 hours, pain scores in Group A were influenced by earlier administration of rescue analgesia because patients in this group required analgesic supplementation sooner than those in the clonidine groups.

Adverse effects such as dry mouth, and mild sedation were more common in the clonidine groups, particularly with the 30 µg dose. However, these adverse effects were mild and manageable. Shivering was observed only in the levobupivacaine-alone group, which may be related to the known anti-shivering properties of clonidine. No patient experienced nausea or vomiting during the study period.

These findings indicate that although higher doses of clonidine provide superior analgesia, they are associated with a greater incidence of hemodynamic adverse effects and therefore require careful monitoring.

Overall, intrathecal clonidine combined with hyperbaric levobupivacaine improved sensory and motor block characteristics and prolonged postoperative analgesia, with greater effects observed at higher doses. Among the studied doses, 30 µg clonidine provided the longest duration of analgesia, although it was associated with a higher incidence of manageable adverse effects.

The present study had certain limitations. First, the sample size was relatively small, which may limit the generalizability of the findings. Second, inclusion of different orthopedic procedures may have introduced variability in postoperative pain perception and analgesic requirements. In addition, only two doses of clonidine were evaluated; therefore, further dose-response studies are required to determine the optimal intrathecal dose that provides effective analgesia with minimal hemodynamic compromise.

CONCLUSION

The present study demonstrates that intrathecal clonidine is an effective adjuvant to 0.5% hyperbaric levobupivacaine for lower limb orthopedic surgeries, significantly improving sensory and motor block characteristics and prolonging postoperative analgesia in a dose-dependent manner. Among the studied doses, clonidine 30 µg provided the longest duration of postoperative analgesia and delayed the requirement for rescue analgesia, although it was associated with a higher incidence of manageable hypotension and bradycardia. Based on the findings of the present study, intrathecal clonidine 30 µg may be considered a useful adjuvant when prolonged postoperative analgesia is desired under appropriate hemodynamic monitoring, whereas the 15 µg dose may be preferable in patients requiring greater hemodynamic stability.

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Table and Figure Legends

Table 1. Baseline Demographic and Clinical Characteristics of Study Participants
Values Are Expressed As Mean ± Standard Deviation Or Number Of Patients. One-Way ANOVA Was Used For Comparison Of Continuous Variables, While Chi-Square Test Was Used For Categorical Variables.

Table 2. Characteristics of Sensory and Motor Blockade and Duration of Analgesia among the Study Groups
ANOVA Was Applied for Intergroup Comparison, Followed by Tukey's Post Hoc Analysis. Significant Intergroup Differences Were Observed Among All Three Groups for Most Sensory Block, Motor Block, and Analgesia-Related Parameters

Table 3. Comparison of Intraoperative Hemodynamic Parameters among the Study Groups
Table 4. Comparison of Postoperative Visual Analog Scale (VAS) Scores Among the Study Groups
Values Are Expressed As Mean ± Standard Deviation. One-Way ANOVA Was Used For Intergroup Comparison.