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Original Research Article

COMPARATIVE STUDY OF BUPRENORPHINE, DEXMEDETOMIDINE AND CLONIDINE AS AN ADJUVANT TO BUPIVACAINE IN SUBARACHNOID BLOCK FOR LOWER LIMB ORTHOPAEDIC SURGERIES

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ABSTRACT

Background: Adjuvants are frequently added to local anesthetics to enhance and prolong spinal anesthesia. Dexmedetomidine, a highly selective α2-adrenergic agonist, has gained attention as a neuraxial adjuvant. This study compared intrathecal dexmedetomidine, clonidine, and buprenorphine combined with 0.5% hyperbaric bupivacaine with respect to block characteristics, hemodynamic effects, postoperative analgesia, and adverse events.

Materials and Methods: In this prospective, randomized, double-blind study, 90 patients undergoing lower limb orthopedic surgeries were allocated into three groups (n=30 each). All patients received 15 mg of 0.5% hyperbaric bupivacaine (total volume 3.5 mL) with either buprenorphine 90 µg (Group B), clonidine 30 µg (Group C), or dexmedetomidine 5 µg (Group D). Sensory and motor block parameters, hemodynamic changes, postoperative pain scores (VAS), duration of analgesia, and complications were evaluated.

Results: Dexmedetomidine produced significantly longer sensory (201.8 min) and motor (339.0 min) block compared to clonidine (141.8 and 267.8 min) and buprenorphine (90.0 and 218.17 min) ($p<0.01$). It also provided prolonged analgesia (365.17 min) and delayed need for rescue analgesics versus clonidine (294.83 min) and buprenorphine (245.5 min). Complication rates were lowest with dexmedetomidine (23.3%), while clonidine was associated with higher hypotension (43.3%) and occasional bradycardia (6.7%).

Conclusion: Intrathecal dexmedetomidine with bupivacaine offers superior and prolonged sensory and motor blockade, improved postoperative analgesia, and better hemodynamic stability compared to clonidine and buprenorphine.

Keywords: α2-adrenergic agonist, bupivacaine, clonidine, dexmedetomidine, buprenorphine, spinal anesthesia.

INTRODUCTION

Subarachnoid block remains one of the most widely practiced regional anesthetic techniques for lower limb surgeries. To enhance the quality and duration of intraoperative and postoperative analgesia, various adjuvants are combined with local anesthetics. However, their routine use is often limited by undesirable side effects or inconsistent postoperative pain relief. Among the available adjuncts, α2-adrenergic agonists have demonstrated promising analgesic benefits when

administered intrathecally with hyperbaric bupivacaine, with relatively minimal adverse effects.

Clonidine, an established α2-adrenergic agonist, has been extensively studied as a neuraxial adjuvant.[1] Dexmedetomidine, a more selective α2-adrenergic agonist, has gained increasing attention in perioperative and critical care practice due to its sedative, analgesic, and sympatholytic properties.[2] Emerging evidence supports its role as a useful adjunct in regional anesthesia, including central neuraxial blocks.[3]

Given the limited but growing body of evidence regarding the efficacy of dexmedetomidine as an intrathecal adjuvant to hyperbaric bupivacaine, the present study was undertaken to further evaluate its clinical utility. Additionally, it aimed to compare dexmedetomidine with commonly used adjuvants such as clonidine and buprenorphine in terms of spinal block characteristics in patients undergoing lower limb surgery. Based on previous human studies,[4-7] it was hypothesized that intrathecal administration of 5 µg dexmedetomidine would result in prolonged postoperative analgesia with favourable block characteristics and minimal side effects.

MATERIALS AND METHODS

After obtaining approval from the Institutional Ethics Committee and securing written informed consent, 90 adult patients of either sex, classified as American Society of Anesthesiologists (ASA) physical status I and II, and scheduled for lower limb surgery under subarachnoid block, were enrolled in this prospective, randomized, double-blind study.

Patients with contraindications to regional anesthesia or significant comorbid conditions such as ischemic heart disease, hypertension, renal impairment, rheumatoid arthritis, or severe hepatic dysfunction were excluded. Pregnant women, chronic alcohol users, malnourished individuals, and patients with atrioventricular block (including incomplete or partial heart block) or those receiving α-blockers were also excluded from participation.

All participants underwent thorough preoperative evaluation one day prior to surgery and were instructed on the use of the Visual Analog Scale (VAS) for postoperative pain assessment. They were advised to fast for 6 hours before surgery and received alprazolam 0.5 mg the night before and 0.25 mg on the morning of surgery as premedication.

Upon arrival in the operating theatre, standard monitoring—including electrocardiography (ECG), pulse oximetry, and noninvasive blood pressure measurement—was instituted, and baseline vital parameters were recorded. Intravenous access was established, and all patients were preloaded with Ringer's lactate solution at a dose of 10 mL/kg.

Participants were randomly allocated in a double-blind manner into three groups of 30 patients each: Group B, Group C, and Group D. Randomization was carried out using a computer-generated random number sequence created through an online randomization program (www.randomizer.org). Group assignments were concealed using sealed opaque envelopes to ensure allocation concealment and maintain blinding. All patients received a total intrathecal volume of 3.5 ml, which included 3 ml (15 mg) of 0.5% hyperbaric bupivacaine hydrochloride (ANAWIN Heavy, Neon). Adjuvants were prepared using an insulin syringe for accuracy. In Group B, patients received 15 mg of 0.5% hyperbaric bupivacaine combined with 90 µg buprenorphine (Buprigesic, Neon), prepared as 0.3 ml of 300 µg/ml buprenorphine plus 0.2 ml normal saline. Group C received 15 mg of 0.5% hyperbaric bupivacaine with 30 µg clonidine (CLONEON, Neon), prepared as 0.2 ml of 150 µg/ml clonidine plus 0.3 ml normal saline. Group D received 15 mg of 0.5% hyperbaric bupivacaine with 5 µg dexmedetomidine (DEXTOMID, Neon), prepared as 0.1 ml of 50 µg/ml dexmedetomidine plus 0.4 ml normal saline.

The study medications were prepared in 5 mL syringes by an anesthesiologist not involved in patient management and were handed over in coded form to the attending anesthesiologist, who remained blinded to group allocation. Subarachnoid block was performed at the L2–L3 or L3–L4 interspace using a 26-gauge Quincke spinal needle with the patient in the sitting position under strict aseptic precautions. After drug administration, patients were positioned supine. Intraoperative observations were recorded by the anesthesiologist performing the block.

The following parameters were documented: onset and duration of sensory block, highest sensory level achieved, time to attain peak sensory level, onset of motor block, time to complete motor block recovery, and total duration of spinal anesthesia. Sensory block onset was defined as the interval between intrathecal injection and loss of pinprick sensation at the T8 dermatome, assessed every 2 minutes. The maximum sensory level was evaluated by pinprick along the midclavicular line at 5-minute intervals for the first 20 minutes and every 15 minutes thereafter. Duration of sensory block was defined as the time taken for regression by two dermatomal segments from the highest level achieved.

Motor blockade was assessed using the modified Bromage scale: 0 = full movement of hip, knee, and ankle; 1 = inability to move hip but able to move knee and ankle; 2 = inability to move hip and knee but able to move ankle; 3 = inability to move hip, knee, and ankle. Onset of motor block was defined as attainment of Bromage score 3, and

complete recovery was considered when the score returned to 0.

The duration of spinal anesthesia was defined as the time from intrathecal injection (considered time zero) to the first complaint of postoperative pain. Surgery commenced after achieving an adequate sensory level up to T8. Hemodynamic parameters were recorded 5 minutes before spinal injection; at 5, 10, 15, 20, and 25 minutes afterward; and subsequently every 15 minutes. Pain was assessed using the Visual Analog Scale (VAS) preoperatively, after surgical incision, at 15-minute intervals intraoperatively, and periodically in the postoperative period.

Intravenous fluids were administered to maintain hemodynamic stability. Hypotension, defined as a reduction in systolic blood pressure greater than 30% from baseline, was treated with 6 mg intravenous ephedrine boluses or crystalloid infusion. Bradycardia (heart rate <50 beats/min) was managed with 0.6 mg intravenous atropine sulfate. Adverse effects such as pruritus, nausea, vomiting, and sedation were recorded. Sedation was assessed using the De Kock sedation scale: 1 = drowsy but responsive to verbal commands; 2 = drowsy, unresponsive to verbal commands but responsive to tactile stimulation; and 3 = unresponsive to both verbal and tactile stimuli.

Following completion of surgery, motor recovery (defined as attainment of modified Bromage score 0) and regression of sensory block were evaluated at 15-minute intervals in the post-anesthesia care unit (PACU). Monitoring of vital parameters and pain assessment using the Visual Analog Scale (VAS) were continued during this period.

Patients reporting a VAS score of 3 or higher received intravenous tramadol 50 mg as rescue analgesia. The total amount of tramadol required by each patient over the subsequent 24 hours was documented and compared among the study groups.

Statistical Analysis

The collected data were tabulated and analyzed using **SPSS version 15.0** (evaluation version). Sample size calculation, based on a power analysis with $\alpha = 0.05$ and $\beta = 1.00$, indicated that 30 patients per group were required to detect a 30-minute difference in median spinal sensory block duration among the groups.

Data were presented as mean ± standard deviation (SD), median with range, or as counts and percentages. Categorical variables—such as sex, ASA class, incidence of nausea/vomiting, use of supplemental analgesia, hypotension, and bradycardia—were analyzed using the **Chi-square test** or **Fisher's exact test**, as appropriate, with significance reported at the 95% confidence interval (CI). Continuous variables, including age and duration of surgery, were compared using **analysis of variance (ANOVA)**. When ANOVA showed significant differences, **Tukey's Honestly Significant Difference (HSD) post hoc test** was applied to determine pairwise group comparisons.

RESULTS

Most of the cases in present study were of Total knee replacement (75%) in all the three groups. Few other cases included were of plating or nailing in femoral fractures cases or high tibial osteotomy in osteoarthritis.

Table 1: Demographic Parameters, Baseline vitals, Duration of Surgery

Parameters	Group B (n= 30)	Group C (n = 30)	Group D (n = 30)	p- value
Age (years)	59.73	56.97	57.13	**0.23**
Female : Male	14:16	21:9	13:17	**0.08**
Body Mass Index (m/kg2)	27.21	26.80	25.63	**0.19**
Heart Rate (per minute)	81.37	87.10	85.10	**0.131**
Mean Arterial Pressure (mm of Hg)	104.90	105.33	104.53	**0.868**
SPO2 (%)	98.43	98.83	98.77	**0.075**
Respiratory Rate (per minute)	17.37	16.33	16.80	**0.11**
Duration of Surgery (minutes)	167.50	161.17	164.40	**0.65**

Data are presented as mean values or counts. Group B = buprenorphine 90 µg, Group C = clonidine 30 µg, Group D = dexmedetomidine 5 µg. SpO_2 = peripheral oxygen saturation; BMI = body mass index. Comparisons were performed using ANOVA for continuous variables and Chi-square or Fisher's exact test for categorical variables.

All patients (n =90) completed the study; There were no statistically significant differences among the three groups regarding age, sex distribution, BMI, baseline vital signs (heart rate, mean arterial pressure, SpO_2, respiratory rate), or duration of surgery ($p > 0.05$ for all), indicating that the groups were comparable at baseline. [Table1]

Table 2: Mean comparison of time of sensory block, motor block and duration of analgesia

Parameters	Group	N	Mean	SD	p- value	p- value
Time of Sensory Block (min)	**B**	30	90.00	23.53	**<0.01**	**B vs C: Sig**
	C	30	141.83	23.76		**C vs D: Sig**
	D	30	201.83	44.34		**B vs D: Sig**
Duration of Analgesia (min)	**B**	30	245.50	25.88	**<0.01**	**B vs C: Sig**
	C	30	294.83	27.99		**C vs D: Sig**

	D	30	365.17	35.46		**B vs D: Sig**
Duration of Motor Block (min)	**B**	30	218.17	24.65	**<0.01**	**B vs C: Sig**
	C	30	267.83	32.26		**C vs D: Sig**
	D	30	339.00	35.27		**B vs D: Sig**

Values are expressed as **Mean ± Standard Deviation (SD)**.

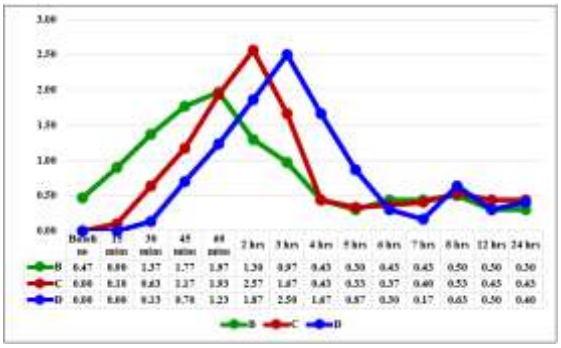
Statistical analysis was performed using **one-way Analysis of Variance (ANOVA)** to compare means among the three groups. Post-hoc pairwise comparisons were carried out using Tukey's Honestly Significant Difference (HSD) test.

A p-value of **< 0.05** was considered statistically significant; $p < 0.01$ indicates a highly significant difference.

Table 2 shows the comparison of time of sensory block, duration of analgesia, and duration of motor block among the three groups. One-way ANOVA demonstrated a statistically highly significant difference among the groups for all three parameters ($p < 0.01$).

The mean time of sensory block was significantly prolonged in Group D (201.83 ± 44.34 min) compared to Group C (141.83 ± 23.76 min) and Group B (90.00 ± 23.53 min). Similarly, the duration of analgesia was longest in Group D (365.17 ± 35.46 min), followed by Group C (294.83 ± 27.99 min), and shortest in Group B (245.50 ± 25.88 min). A comparable pattern was observed for duration of motor block, with Group D (339.00 ± 35.27 min) showing significantly greater prolongation than Group C (267.83 ± 32.26 min) and Group B (218.17 ± 24.65 min).

Post-hoc analysis revealed statistically significant differences between all pairwise comparisons (B vs C, C vs D, and B vs D), indicating a stepwise and significant increase in block characteristics and analgesia duration from Group B to Group D.



Graph 3: VAS Score Comparison

The most effective pain control during the first intraoperative hour was observed in the dexmedetomidine group, followed by the clonidine group. In contrast, patients in the buprenorphine group demonstrated the highest Visual Analogue Scale (VAS) scores during the first postoperative hour. Rescue analgesia was administered according to patient demand. The time to first rescue analgesic requirement was shortest in the buprenorphine group and longest in the dexmedetomidine group, consistent with the significant intergroup difference in duration of analgesia ($p < 0.05$). [Graph1]

Table 3: Comparison of the incident complications between the groups

Complications	**Group**			**Total**	**p- value**
	B	**C**	**D**		
None	14	15	23	52	**0.036**
	46.7%	50.0%	76.7%	86.7%	
Bradycardia	0	2	0	2	**0.13**
	0.0%	6.7%	0.0%	3.3%	
Hypotension	0	13	3	16	**<0.01**
	0.0%	43.3%	10.0%	26.7%	
Pruritis	2	0	0	2	**0.13**
	6.7%	0.0%	0.0%	3.3%	
Sedation	9	0	4	13	**<0.01**
	30.0%	0.0%	13.3%	21.7%	
Sedation & Hypotension	1	0	0	1	**0.37**
	3.3%	0.0%	0.0%	1.7%	
Sedation & Pruritis	4	0	0	4	**0.015**
	13.3%	0.0%	0.0%	6.7%	

Values are expressed as number (percentage).

Intergroup comparisons were performed using the **Chi-square test**.

When expected cell counts were less than 5, **Fisher's exact test** was applied.

A p-value of **< 0.05** was considered statistically significant.

Table 3 demonstrates a significant difference in the overall incidence of complications among the groups ($p = 0.036$). The highest proportion of patients without complications was observed in Group D (76.7%). Hypotension occurred significantly more frequently in Group C (43.3%) compared to the other groups ($p < 0.01$). Sedation was significantly higher in Group B (30.0%) ($p < 0.01$), and the combination of sedation with pruritus was noted exclusively in Group B ($p = 0.015$). Differences in bradycardia, isolated

pruritus, and combined sedation with hypotension were not statistically significant.

DISCUSSION

Our study simultaneously compared three intrathecal adjuvants, unlike previous investigations that primarily evaluated dexmedetomidine against a single comparator. Additionally, we assessed the analgesic efficacy of intrathecal dexmedetomidine, an area that has been sparsely explored in the literature.[7] The findings demonstrate that the addition of 5 µg dexmedetomidine to spinal bupivacaine significantly prolonged both sensory and motor blockade when compared with 90 µg buprenorphine and 30 µg clonidine administered intrathecally. Furthermore, the overall quality and duration of analgesia were superior in the dexmedetomidine group compared with the other study groups, indicating its enhanced efficacy as a spinal adjuvant.

The exact mechanism by which intrathecal α_2-adrenoreceptor agonists prolong sensory and motor blockade of local anesthetics remains largely speculative. It is likely due to additive or synergistic effects arising from the distinct mechanisms of action of local anesthetics and α_2-agonists. Local anesthetics primarily act by blocking voltage-gated sodium channels, whereas α_2-adrenoreceptor agonists bind to presynaptic C-fibers and postsynaptic dorsal horn neurons. They produce analgesia by inhibiting the release of C-fiber neurotransmitters and hyperpolarizing postsynaptic dorsal horn neurons.[4,5,8] The complementary actions of these agents contribute to their profound analgesic properties. The prolongation of motor block may result from the binding of α_2-agonists to motor neurons within the dorsal horn.[4,5] Dexmedetomidine, being approximately eight times more selective for α_2-adrenoreceptors than clonidine, provides enhanced efficacy with a favorable safety profile, making it a valuable adjunct in a variety of clinical settings.[9,10]

The use of dexmedetomidine as an epidural adjunct has been investigated by several authors, who have reported its synergistic effect with local anesthetics. It has been shown to prolong the duration of motor and sensory blockade as well as postoperative analgesia without increasing morbidity.[11,12] Clinical studies further demonstrate that neuraxial administration of dexmedetomidine potentiates the effects of local anesthetics, reduces intraoperative anesthetic requirements, helps prevent intraoperative awareness, improves intraoperative oxygenation, and enhances postoperative analgesia when used epidurally or caudally in conjunction with general anesthesia.[13,14,15]

Most clinical experience with intrathecal α_2-adrenoreceptor agonists has been reported with clonidine, highlighting a need for further studies evaluating the efficacy, safety, and optimal dosing of intrathecal dexmedetomidine as a supplement to spinal local anesthetics.[16,17,18,19] In our study, the intrathecal dose of dexmedetomidine was selected based on prior human studies in which no neurotoxic effects were observed. Kanazi et al.[4] demonstrated that 3 µg of dexmedetomidine or 30 µg of clonidine added to 13 mg of spinal bupivacaine produced comparable durations of sensory and motor blockade with minimal side effects in patients undergoing urological surgery. Based on these findings, we considered 3–5 µg of dexmedetomidine to be approximately equipotent to 30–45 µg of clonidine for supplementation of spinal bupivacaine.[4,5]

The time of onset of sensory block was comparable among all groups in our study (D group=8.1±2.1, C group=8.1±2.5 and B group 8.5±1.7.) These results are consistent with Al Ghanem et al.,[5] who reported no significant difference in onset time between patients receiving dexmedetomidine (7.5 ± 7.4 min) and fentanyl (7.4 ± 3.3 min) as adjuvants to isobaric bupivacaine (P = 0.95). The slightly shorter onset times in their study may be explained by differences in bupivacaine type (isobaric vs hyperbaric), definition of onset (T10 dermatome vs T8 in our study), and patient positioning (lithotomy vs supine in our study). Similarly, Kanazi et al,[4] observed comparable onset times when comparing 3 µg dexmedetomidine with 30 µg clonidine, and Gupta et al,[7] reported similar findings with 5 µg dexmedetomidine versus 25 µg fentanyl as spinal adjuvants. These studies, consistent with our results, also noted a significantly prolonged time for two-segment sensory regression in the dexmedetomidine groups, indicating extended duration of analgesia.

The intrathecal administration of 5 µg dexmedetomidine in our study produced a motor block onset comparable to the other groups (D group= 9.0±3.0 C group=9.8±3.6 B group 9.7±3.2), but with a significantly prolonged duration of motor blockade. [Table 2] These findings are consistent with previous investigations comparing dexmedetomidine with various adjuvants, including clonidine, fentanyl, and sufentanil.[4-7,23] In our study, the mean duration of motor block was notably longer (273.3 ± 24.6 min) compared with 250 ± 76 min reported by Kanazi et al,[4] and 240 ± 64 min reported by Al Ghanem et al,[5] (both $P < 0.001$). This difference may be attributed to the higher intrathecal volume of drug (3.5 ml) used in our study, compared with 1.9 ml and 2.5 ml in the respective studies.

In our study, the requirement for first rescue analgesia was significantly delayed, and the total 24-hour rescue analgesic consumption was markedly reduced in patients receiving 5 µg intrathecal dexmedetomidine compared with 30 µg clonidine and 90 µg buprenorphine, highlighting its superior analgesic efficacy as a spinal adjuvant.

Similar findings were reported by Gupta et al,[7] who observed significantly enhanced analgesia with dexmedetomidine compared to fentanyl when used intrathecally ($P < 0.001$). Additionally, studies by Al-Mustafa et al,[6] and Hala EA Eid et al,[21] demonstrated a dose-dependent prolongation of sensory and motor blockade, along with reduced postoperative analgesic requirements, with increasing intrathecal dexmedetomidine doses (5, 10, and 15 µg).

The most commonly reported side effects of intrathecal α_2-adrenoreceptor agonists are bradycardia and hypotension. In our study, these adverse effects were minimal, likely due to the use of small intrathecal doses of dexmedetomidine, clonidine, and 90 µg buprenorphine in combination with relatively high doses of local anesthetics. However, hypotension occurred significantly more frequently in Group C (43.3%) compared to the other groups ($p < 0.01$). Sedation was significantly higher in Group B (30.0%) ($p < 0.01$), and the combination of sedation with pruritus was noted exclusively in Group B ($p = 0.015$). Differences in bradycardia, isolated pruritus, and combined sedation with hypotension were not statistically significant at these low adjuvant doses, the near-maximal sympatholysis produced by the local anesthetic was not further potentiated. The small doses may also explain the minimal or absent sedation observed across all groups. In contrast, a 15 µg intrathecal dose of dexmedetomidine, as reported by Hala EA Eid et al,[21] produced significantly higher sedation scores, which may be advantageous for lengthy or complex procedures by reducing the need for intravenous sedatives. However, excessive sedation at higher doses may pose risks in elderly or high-risk surgical patients due to potential respiratory depression. Pruritus associated with intrathecal fentanyl was observed in a few patients but was not statistically significant.

Although this study adds to the current knowledge on dexmedetomidine, the results should be considered taking into consideration the obvious limitations: First, the sample size was relatively small, which may limit the generalizability of the findings. Second, the study focused exclusively on lower limb surgeries and may not reflect outcomes in other surgical populations or procedures requiring different sensory levels. Third, we evaluated only a single dose of each adjuvant (5 µg dexmedetomidine, 30 µg clonidine, 90 µg buprenorphine), so dose-response relationships could not be assessed comprehensively. Fourth, the study was limited to intraoperative and 24-hour postoperative observations; longer-term outcomes such as delayed neurotoxicity or persistent analgesic effects were not assessed. Finally, while objective measures of block characteristics were recorded, patient-reported outcomes such as satisfaction and functional recovery were not formally evaluated.

Our study demonstrates that intrathecal dexmedetomidine is a highly effective adjuvant to bupivacaine, offering superior sensory and motor block prolongation and enhanced postoperative analgesia compared with buprenorphine and clonidine. Its favorable intrathecal anesthetic and analgesic profile, combined with minimal side effects, makes it an attractive option for long-duration surgical procedures. However, the prolonged motor blockade associated with dexmedetomidine may limit its use in short-duration or ambulatory surgeries, where rapid recovery of motor function is desirable.

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