European Journal of Clinical Pharmacy
Print ISSN: 2385-409X, **Online ISSN**: 3105-0409
Website: https://farmclin.com/

Dexmedetomidine versus Clonidine as Adjuvant to Spinal Anesthesia: A Prospective Randomized Double-Blind Comparative Study of Block Characteristics and Hemodynamic Stability

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Received: 10-01-2026
Revised: 26-02-2026
Accepted: 19-02-2026
Published: 06-03-2026

Abstract: Background and Aims: Alpha-2 adrenergic agonists enhance spinal anesthesia when used as intrathecal adjuvants. This study compared dexmedetomidine and clonidine as adjuvants to hyperbaric bupivacaine for spinal anesthesia with respect to block characteristics, postoperative analgesia, and hemodynamic stability.**Methods:** In this prospective, randomized, double-blind study, 180 patients (ASA I–II) scheduled for lower limb and infraumbilical surgeries were allocated into three groups of 60 each. Group D received 0.5% hyperbaric bupivacaine 2.5 mL with dexmedetomidine 5 µg; Group C received the same bupivacaine with clonidine 30 µg; and Group S (control) received bupivacaine with 0.5 mL normal saline. Onset and duration of sensory and motor block, time to first analgesic request, hemodynamic parameters, sedation score, and side effects were recorded.**Results:** Onset of sensory and motor block was faster in Group D compared with Group C and Group S ($p < 0.001$). Duration of sensory block (214.6 ± 18.3 min vs. 186.2 ± 21.4 min vs. 142.8 ± 19.6 min) and motor block were significantly prolonged in Group D ($p < 0.001$). Time to first analgesic request was longest in Group D (312.4 ± 32.6 min; $p < 0.001$). Both adjuvant groups showed significantly higher sedation scores and lower rates of shivering compared to control. Hypotension and bradycardia were more frequent in Groups D and C than Group S, with no significant difference between the two adjuvant groups ($p > 0.05$).**Conclusion:** Intrathecal dexmedetomidine 5 µg is superior to clonidine 30 µg as an adjuvant to hyperbaric bupivacaine in terms of faster onset, prolonged sensory and motor block, and longer postoperative analgesia, with comparable hemodynamic stability and side-effect profiles.

Keywords: Dexmedetomidine; Clonidine; Intrathecal adjuvant; Spinal anesthesia; Bupivacaine; Regional anesthesia; Postoperative analgesia; Alpha-2 agonist

INTRODUCTION

Spinal anesthesia remains one of the most widely employed neuraxial techniques for surgeries involving the lower abdomen, pelvis, and lower extremities. Its popularity derives from rapid onset, reliable surgical conditions, cost-effectiveness, and the ability to avoid the systemic risks associated with general anesthesia.1,2 However, its duration is limited, and postoperative pain management after resolution of the block frequently remains an unmet challenge in resource-limited settings.

To overcome these limitations, various adjuvants have been added to local anesthetics in spinal anesthesia, including opioids, alpha-2 adrenergic agonists, neostigmine, ketamine, and magnesium sulfate.3,4 Among these, alpha-2 adrenergic agonists have garnered particular interest because of their ability to prolong both sensory and motor block and provide postoperative analgesia without the adverse respiratory effects associated with intrathecal opioids. Clonidine, a partial alpha-2 agonist with an alpha-2 to alpha-1 selectivity ratio of 220:1, has been studied extensively as an intrathecal adjuvant since the 1980s.5 Its mechanism of action involves activation of alpha-2 adrenoceptors in the dorsal horn of the spinal cord, resulting in inhibition of substance P release and hyperpolarization of post-synaptic membranes, thereby enhancing nociceptive block and prolonging the duration of spinal anesthesia.6

Dexmedetomidine is a highly selective and specific alpha-2 agonist with an alpha-2 to alpha-1 selectivity ratio of 1620:1 — approximately eight-fold more selective than clonidine.7 Originally approved for intravenous sedation in intensive care and procedural settings, dexmedetomidine has more recently attracted attention as an intrathecal adjuvant. Preclinical studies have demonstrated that dexmedetomidine produces dose-dependent antinociception when administered intrathecally, without evidence of neurotoxicity.8

The pharmacokinetic profile of intrathecal dexmedetomidine is characterized by rapid onset, resulting from high lipid solubility, and a longer duration of action compared with clonidine when used in equianalgesic doses.9 Kanazi et al. were among the first to demonstrate that intrathecal dexmedetomidine 3 µg significantly prolonged sensory and motor blocks produced by hyperbaric bupivacaine, and that its effects were superior to those of clonidine 30 µg.10

Despite these encouraging results, the comparative literature on dexmedetomidine versus clonidine specifically with respect to hemodynamic stability — a primary clinical concern during spinal anesthesia — remains limited and sometimes contradictory. Hypotension and bradycardia, consequences of sympatholysis, are well-recognized complications of both agents when administered intrathecally, but the relative magnitude and clinical significance of these effects at commonly used doses require further characterization.11,12

The present study was designed as a prospective, randomized, double-blind, three-arm trial to compare intrathecal dexmedetomidine 5 µg and clonidine 30 µg as adjuvants to hyperbaric bupivacaine with respect to: (1) onset and duration of sensory block; (2) onset and duration of motor block; (3) maximum dermatomal level of sensory analgesia; (4) duration of postoperative analgesia; (5) intraoperative hemodynamic stability; and (6) incidence of side effects including sedation, shivering, nausea, and vomiting.

Materials and Methods

Study Design and Ethics

This prospective, randomized, double-blind, placebo-controlled study was conducted in the Department of Anaesthesiology and Critical Care at a tertiary care

teaching institution over a period of 18 months. The study protocol was approved by the Institutional Ethics Committee (Reference No. IEC/2023/48) and registered with the Clinical Trials Registry–India (CTRI/2023/07/054682). Written informed consent was obtained from all participants prior to enrollment. The study was conducted in conformity with the Declaration of Helsinki (revised 2013).

Sample Size Calculation

Sample size was computed based on a prior study by Mahendru et al.,13 which reported a mean duration of sensory block of 186 ± 21 min with intrathecal clonidine. Assuming a clinically significant difference of 20 min between the dexmedetomidine and clonidine groups, with a standard deviation of 25 min, type I error (α) of 0.05, and power of 80%, a minimum of 50 patients per group was required. Accounting for 15% dropout, 60 patients per group were enrolled, yielding a total of 180 patients.

Inclusion and Exclusion Criteria

Patients aged 18–65 years, of either sex, classified as American Society of Anesthesiologists (ASA) physical status I or II, weighing 50–90 kg, and scheduled for elective lower limb or infraumbilical surgeries of anticipated duration 60–120 minutes were eligible for inclusion. Exclusion criteria included: patient refusal; known allergy to study drugs; contraindications to spinal anesthesia (coagulopathy, local infection, raised intracranial pressure); hemodynamic instability (baseline systolic blood pressure < 100 mmHg or heart rate < 60 beats per minute [bpm]); pre-existing neurological disorders; pregnancy; severe cardiac, hepatic, or renal disease; chronic pain syndromes or preoperative analgesic use; body mass index > 35 kg/m²; and inability to communicate for assessment of sedation and pain scores.

Randomization and Blinding

Randomization was performed using a computer-generated random number table in blocks of six, and allocation was concealed using sequentially numbered, opaque, sealed envelopes. An anesthesiologist not involved in patient care prepared the study solutions and was not present during the intraoperative period. The attending anesthesiologist and all outcome assessors were blinded to group allocation throughout the study period. The study solutions were prepared to identical volumes (0.5 mL) and appearances.

Study Groups and Drug Preparation

Patients were randomly allocated to one of three groups (n = 60 per group):

- Group D: Hyperbaric bupivacaine 0.5% 2.5 mL (12.5 mg) + dexmedetomidine 5 µg in 0.5 mL preservative-free normal saline (total volume 3.0 mL)
- Group C: Hyperbaric bupivacaine 0.5% 2.5 mL (12.5 mg) + clonidine 30 µg in 0.5 mL preservative-free normal saline (total volume 3.0 mL)
- Group S (Control): Hyperbaric bupivacaine 0.5% 2.5 mL (12.5 mg) + 0.5 mL preservative-free normal saline (total volume 3.0 mL)

Dexmedetomidine (Precedex®, Pfizer, India) 200 µg/2 mL was diluted to a concentration of 10 µg/mL with normal saline, and 0.5 mL of this solution was used to provide a dose of 5 µg. Clonidine (Catapres®, Boehringer Ingelheim) 150 µg/mL was diluted to 60 µg/mL and 0.5 mL used to provide 30 µg.

Anesthetic Technique

All patients received standard monitoring including five-lead electrocardiography, non-invasive blood pressure measurement, and pulse oximetry. An intravenous (IV) access was established with an 18G cannula, and a preload of Ringer's lactate 10 mL/kg was administered over 15 minutes before the spinal procedure. Baseline hemodynamic parameters were recorded.

With the patient in the sitting position, lumbar puncture was performed at the L3–L4 or L4–L5 interspace using a 25G Quincke spinal needle under strict aseptic precautions. After free flow of clear cerebrospinal fluid, the study drug solution was injected over 15–20 seconds at a rate of approximately 0.2 mL/second. The patient was placed supine immediately after the injection. Supplemental oxygen at 4 L/min via facemask was administered to all patients intraoperatively. In the event of hemodynamic compromise, IV ephedrine 6 mg boluses were administered for hypotension (SBP < 90 mmHg or a fall > 20% from baseline), and IV atropine 0.6 mg for symptomatic bradycardia (HR < 50 bpm).

Outcome Measures

Sensory block assessment: Sensory block was assessed bilaterally using a 23G hypodermic needle for the pinprick test every minute for the first 10 minutes and every 2 minutes thereafter. The highest dermatomal level was recorded. Duration of sensory block was defined as the time from intrathecal injection to regression of the sensory block to the S2 dermatome.

Motor block assessment: Motor block of the lower limbs was graded using the modified Bromage scale (0 = no motor block; 1 = inability to raise extended leg; 2 = inability to flex knee; 3 = inability to flex ankle). Onset was defined as the time to achieve Bromage grade 3. Duration of motor block was defined as the time from injection to return of complete motor function (Bromage grade 0).

Postoperative analgesia: Pain was assessed using the Visual Analogue Scale (VAS) at regular intervals in the postoperative period. Time to first analgesic request was defined as the time from intrathecal injection to the first postoperative complaint of pain (VAS ≥ 4) requiring rescue analgesia with IV paracetamol 1 g.

Sedation: Intraoperative sedation was assessed using the Ramsay Sedation Scale (RSS): 1 = anxious/agitated; 2 = cooperative/orientated/tranquil; 3 = responds to commands only; 4 = brisk response to glabellar tap or loud stimulus; 5 = sluggish response; 6 = unresponsive. RSS ≥ 2 was considered clinically meaningful sedation.

Hemodynamic parameters: Heart rate (HR) and non-invasive blood pressure were recorded at baseline, 2, 5, 10, 15, 20, 30, 45, and 60 minutes after intrathecal injection and at 15-minute intervals thereafter. Hypotension was defined as SBP < 90 mmHg or a fall > 20% from baseline. Bradycardia was defined as HR < 50 bpm.

Additional recorded outcomes included: incidence of nausea and vomiting (managed with IV ondansetron 4 mg), shivering (four-point scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe), pruritus, and respiratory depression (SpO_2 < 94%).

Statistical Analysis

Statistical analyses were performed using SPSS® version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) and compared using one-way ANOVA with post-hoc Tukey's test for multiple group comparisons. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Repeated hemodynamic measurements were analyzed using repeated-measures ANOVA. A two-tailed p-value < 0.05 was considered statistically significant.

Results

Patient Demographics

A total of 197 patients were screened, of whom 17 were excluded (8 declined participation, 5 did not meet inclusion criteria, 4 were withdrawn after enrollment). The remaining 180 patients completed the study and were included in the final analysis. No significant differences were found among the three groups with respect to age, weight, height, sex distribution, ASA physical status, or duration of surgery (Table 1).

Table 1: Demographic and Clinical Characteristics of Study Groups

Characteristic	Group D (n=60)	Group C (n=60)	Group S (n=60)	p-value
Age (years)	38.4 ± 11.2	39.8 ± 12.4	37.6 ± 10.8	0.721
Weight (kg)	68.6 ± 9.4	70.2 ± 10.1	67.8 ± 8.7	0.534
Height (cm)	166.4 ± 7.8	167.2 ± 8.2	165.8 ± 7.4	0.642
Sex (M/F)	34/26	32/28	33/27	0.942
ASA I/II	38/22	36/24	37/23	0.891
Duration of surgery (min)	72.4 ± 18.6	74.2 ± 19.4	71.8 ± 17.2	0.774

Values are mean ± SD or number (%). No significant differences among groups (p > 0.05).

Block Characteristics

The onset of sensory block was significantly faster in Group D (2.8 ± 0.6 min) compared with Group C (3.4 ± 0.7 min) and Group S (4.2 ± 0.9 min) (p < 0.001). Similarly, onset of motor block was achieved more rapidly in Group D (4.6 ± 1.1 min) than in Group C (5.4 ± 1.2 min) and Group S (6.8 ± 1.4 min). The maximum sensory level attained was higher in Group D (median T4) compared with Group C (T5) and Group S (T6) (p = 0.018).

Duration of sensory block was significantly longer in Group D (214.6 ± 18.3 min) versus Group C (186.2 ± 21.4 min) versus Group S (142.8 ± 19.6 min) (p < 0.001). Duration of motor block followed a similar pattern: Group D 196.4 ± 17.1 min; Group C 168.7 ± 19.8 min; Group S 128.4 ± 16.3 min (p < 0.001). Post-hoc analysis revealed statistically significant differences between all pairwise group comparisons for both sensory and motor duration (p < 0.01 for each).

The time to first analgesic request was significantly prolonged in Group D (312.4 ± 32.6 min) compared with Group C (261.8 ± 28.4 min) and Group S (186.2 ± 24.7 min) (p < 0.001). Detailed block characteristics are summarized in Table 2.

Table 2: Comparison of Block Characteristics and Postoperative Analgesia

Parameter	Group D (Dexmedetomidine)	Group C (Clonidine)	Group S (Control)	p-value
Onset of sensory block (min)	2.8 ± 0.6	3.4 ± 0.7	4.2 ± 0.9	<0.001

Max sensory level (dermatomal)	T4 (T3–T5)	T5 (T4–T6)	T6 (T5–T7)	0.018
Duration of sensory block (min)	214.6 ± 18.3	186.2 ± 21.4	142.8 ± 19.6	<0.001
Duration of motor block (min)	196.4 ± 17.1	168.7 ± 19.8	128.4 ± 16.3	<0.001
Time to first analgesic request (min)	312.4 ± 32.6	261.8 ± 28.4	186.2 ± 24.7	<0.001
Onset of motor block (min)	4.6 ± 1.1	5.4 ± 1.2	6.8 ± 1.4	<0.001

Values are mean ± SD or median (range). Group D: Dexmedetomidine; Group C: Clonidine; Group S: Normal saline (control).

Hemodynamic Parameters and Side Effects

Both adjuvant groups exhibited a significantly higher incidence of bradycardia compared with control (Group D: 23.3%; Group C: 28.3%; Group S: 8.3%; p = 0.011). The incidence of hypotension requiring ephedrine was numerically higher in Groups D and C compared with Group S, but this difference did not reach statistical significance (p = 0.072). No significant difference was observed between Groups D and C for either hypotension or bradycardia (p > 0.05).

Intraoperative sedation scores were significantly higher in both adjuvant groups (RSS ≥ 2: Group D 53.3%; Group C 36.7%) compared with control (10%; p < 0.001), with Group D demonstrating deeper sedation than Group C (p = 0.041). The incidence of shivering was significantly lower in both adjuvant groups compared with control (p = 0.041). No patient in any group developed respiratory depression (SpO_2 < 94%). Nausea occurred in 4 patients (Group D: 2; Group C: 1; Group S: 1), and pruritus was reported in 3 patients (Group D: 2; Group C: 1), with no statistically significant between-group differences. Hemodynamic parameters and side effect data are summarized in Table 3.

Table 3: Hemodynamic Parameters and Adverse Effects

Parameter	Group D	Group C	Group S	p-value
Incidence of hypotension (%)	18 (30%)	21 (35%)	10 (16.7%)	0.072
Incidence of bradycardia (%)	14 (23.3%)	17 (28.3%)	5 (8.3%)	0.011
Mean HR nadir (bpm)	56.4 ± 6.2	58.2 ± 7.1	68.4 ± 5.8	<0.001
Mean SBP nadir (mmHg)	94.6 ± 8.3	92.8 ± 9.1	102.4 ± 7.6	0.003
Ephedrine required (n, %)	18 (30%)	21 (35%)	10 (16.7%)	0.072
Shivering (n, %)	4 (6.7%)	3 (5%)	12 (20%)	0.041
Sedation score ≥ 2 (n, %)	32 (53.3%)	22 (36.7%)	6 (10%)	<0.001

Values are mean ± SD or number (%). HR: Heart rate; SBP: Systolic blood pressure.

DISCUSSION

The principal finding of this study is that intrathecal dexmedetomidine 5 µg provides superior spinal block characteristics compared with intrathecal clonidine 30 µg when used as an adjuvant to hyperbaric bupivacaine 0.5% for lower limb and infraumbilical surgeries. This superiority is manifested as a significantly faster onset, higher maximum sensory level, prolonged duration of both sensory and motor block, and a substantially longer duration of postoperative analgesia. These findings are consistent with the greater alpha-2 receptor selectivity of dexmedetomidine and corroborate the results of several earlier investigations.10,13,14

The mechanism by which alpha-2 agonists enhance spinal anesthesia is multifactorial. Their primary site of action within the spinal cord is the substantia gelatinosa (lamina II) of the dorsal horn, where activation of alpha-2 adrenoceptors inhibits the release of excitatory neurotransmitters — particularly substance P, calcitonin gene-related peptide, and glutamate — and hyperpolarizes post-synaptic neurons via G-protein-coupled inwardly rectifying potassium (GIRK) channels.5,6 In addition, both agents modulate C-fiber conduction by acting on alpha-2B receptors on peripheral terminals of sensory neurons. The superior potency of dexmedetomidine at alpha-2 receptors translates into more pronounced inhibition of nociceptive transmission, explaining the more rapid onset and prolonged duration observed in Group D.7,8

The faster onset of sensory block observed with dexmedetomidine (2.8 ± 0.6 min) compared with clonidine (3.4 ± 0.7 min) in the current study is consistent with published data. Kanazi et al.10 reported onset times of 3.3 ± 0.4 min and 4.3 ± 0.7 min with intrathecal dexmedetomidine 3 µg and clonidine 30 µg, respectively. Similarly, Mahendru et al.13 demonstrated that dexmedetomidine provided faster onset compared to clonidine and fentanyl when each was combined with bupivacaine spinal anesthesia. The slightly faster onset in our study compared with earlier reports may reflect the higher dexmedetomidine dose (5 µg vs. 3 µg) employed.

The prolongation of sensory and motor block observed with both adjuvants in the current study aligns with the well-established pharmacological actions of alpha-2 agonists on spinal cord neurons. Eid et al.15 demonstrated a dose-dependent prolongation of hyperbaric bupivacaine spinal anesthesia by intrathecal dexmedetomidine, while Strebel et al.16 similarly reported dose-related extension of bupivacaine spinal block by intrathecal clonidine. The significant advantage of dexmedetomidine over clonidine in prolonging both sensory and motor block observed in our study (by approximately 28 minutes for sensory and 28 minutes for motor block) is likely attributable to its greater receptor affinity and possibly its slower dissociation from alpha-2 receptors.

The prolongation of postoperative analgesia represents perhaps the most clinically significant finding of this study. The time to first analgesic request was 312.4 ± 32.6 min in Group D — approximately 50 minutes longer than in Group C (261.8 ± 28.4 min) and more than 2.5 hours longer than in the control group (186.2 ± 24.7 min). This finding is of direct relevance to clinical practice, particularly in settings where postoperative analgesic resources may be limited. Gupta et al.17 reported similar findings in a randomized controlled trial comparing intrathecal dexmedetomidine and fentanyl as adjuvants to bupivacaine, with dexmedetomidine providing significantly longer postoperative analgesia.
Regarding hemodynamic stability, both dexmedetomidine and clonidine were associated with a higher incidence of bradycardia compared with control. This is consistent with their sympatholytic mechanism of action: stimulation of alpha-2 receptors in the nucleus tractus solitarius and lateral reticular nucleus results in reduced sympathetic outflow and enhanced vagal tone, producing dose-dependent decreases in HR and BP.6 However, no statistically significant difference was observed between Group D and Group C for either hypotension or bradycardia — a finding of practical importance. The concern that the greater receptor selectivity of dexmedetomidine might translate into more pronounced hemodynamic depression does not appear to be borne out at the doses employed in this study. This is consistent with the meta-analysis by Abdallah et al.,18 which found that intravenous dexmedetomidine as an adjunct to spinal anesthesia was associated with reduced HR and BP but concluded that the hemodynamic effects were clinically manageable and consistent with those of other alpha-2 agonists.

The significantly higher incidence of intraoperative sedation in Group D (RSS ≥ 2: 53.3%) compared with Group C (36.7%) may be viewed as either an advantage or a disadvantage, depending on clinical context. In anxious patients or for procedures requiring relative immobility, the sedative properties of dexmedetomidine may be beneficial and reduce the need for supplemental intravenous sedation. Conversely, the potential for deeper sedation necessitates careful neurological and respiratory monitoring, even though no patient in this study developed respiratory depression. The sedative effect of both adjuvants is mediated through alpha-2 receptors in the locus coeruleus, the principal noradrenergic nucleus in the central nervous system.19

Both dexmedetomidine and clonidine significantly reduced the incidence of shivering compared with the saline control group. This finding is consistent with established evidence that alpha-2 agonists lower the thermoregulatory threshold for shivering through a combination of central and spinal mechanisms. Bajwa et al.20 similarly reported a significantly lower shivering rate with epidural dexmedetomidine compared with clonidine, attributing this in part to the greater alpha-2 selectivity and potency of dexmedetomidine.

Several limitations of this study deserve acknowledgment. First, the study was conducted at a single center, which may limit generalizability. Second, doses were not adjusted for patient weight or height, and the fixed-dose approach may introduce variability. Third, continuous monitoring of sedation and respiratory rate in the postoperative period was limited to two hours; thus, late-onset respiratory events cannot be entirely excluded. Fourth, we did not assess the quality of the block using more granular tools such as current perception threshold testing. Finally, the optimal dose of intrathecal dexmedetomidine remains to be definitively established, and future dose-finding studies are warranted.

CONCLUSION

Intrathecal dexmedetomidine 5 µg is a more efficacious adjuvant to hyperbaric bupivacaine 0.5% spinal anesthesia than clonidine 30 µg, providing significantly faster onset of sensory and motor block, higher maximum sensory level, prolonged duration of both sensory and motor block, and substantially longer postoperative analgesia. The hemodynamic profiles and incidence of adverse effects are comparable between the two adjuvants, with both producing a clinically manageable increase in bradycardia relative to spinal anesthesia without adjuvant. The deeper intraoperative sedation associated with dexmedetomidine may confer additional benefit in selected patients but requires appropriate monitoring. Based on these findings, intrathecal dexmedetomidine 5 µg can be recommended as a preferred alpha-2 agonist adjuvant for spinal anesthesia in lower limb and infraumbilical

surgeries.

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