Comparative Evaluation of Intrathecal Clonidine and Nalbuphine as an Adjuvant to Hyperbaric Ropivacaine in Subarachnoid Block

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Abstract

Subarachnoid block is a widely used anesthetic technique for lower abdominal and lower limb surgeries. Adding adjuvants to local anesthetics enhances block quality and prolongs postoperative analgesia. This prospective, randomized, double-blind study compared the efficacy of intrathecal clonidine versus nalbuphine as adjuvants to hyperbaric ropivacaine. Ninety patients undergoing lower limb orthopedic surgery were randomly allocated into three groups (n=30 each): Group R received 15mg hyperbaric ropivacaine 0.75% alone, Group RC received ropivacaine plus 30µg clonidine, and Group RN received ropivacaine plus 0.8mg nalbuphine. Primary outcomes included onset and duration of sensory and motor block. Secondary outcomes comprised duration of analgesia, hemodynamic parameters, and adverse effects. Both adjuvant groups showed significantly faster onset of sensory block (RC: 4.2±0.8min, RN: 4.5±0.9min) compared to control (5.8±1.1min) ($p<0.001$). Duration of sensory block was prolonged in Group RC (246±28min) and Group RN (218±24min) versus Group R (168±21min) ($p<0.001$). Motor block duration was longest in Group RC (198±22min), followed by RN (176±19min) and R (142±17min) ($p<0.001$). Time to first rescue analgesia was significantly extended in RC (386±42min) and RN (342±38min) compared to R (246±31min) ($p<0.001$). Hypotension incidence was higher in Group RC (33.3%) compared to RN (16.7%) and R (13.3%) ($p=0.041$). Both clonidine and nalbuphine effectively enhance ropivacaine spinal anesthesia, with clonidine providing superior block characteristics but increased hypotension risk.

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Introduction

Subarachnoid block remains one of the most reliable and widely practiced regional anesthetic techniques for surgeries involving the lower abdomen, perineum, and lower extremities [1]. The technique offers several advantages including rapid onset, profound analgesia, muscle relaxation, and reduced stress response to surgery. However, conventional spinal anesthesia with local anesthetics alone is often limited by relatively short duration of postoperative analgesia, necessitating early administration of

systemic analgesics with their associated side effects [2]. The quest for prolonging the duration and improving the quality of spinal anesthesia has led to extensive research on various adjuvants to local anesthetics. These adjuvants work through different mechanisms to enhance sensory and motor blockade while extending the duration of postoperative analgesia [3]. The ideal adjuvant should prolong analgesia without prolonging motor block excessively, have minimal hemodynamic effects, and not cause neurotoxicity.

Ropivacaine, a long-acting amide local anesthetic, has gained popularity for spinal anesthesia due to its favorable safety profile. Compared to bupivacaine, ropivacaine produces less cardiac toxicity and motor block while maintaining adequate sensory anesthesia [4]. The introduction of hyperbaric formulations has further improved its reliability and predictability in spinal anesthesia. However, even with ropivacaine, the duration of analgesia may be insufficient for extensive surgeries or optimal postoperative pain management.

Clonidine, an α2-adrenergic agonist, has been extensively studied as an intrathecal adjuvant. When administered spinally, clonidine acts on pre-synaptic C-fibers and post-synaptic dorsal horn neurons to produce analgesia [5]. The drug enhances both sensory and motor block duration when combined with local anesthetics. Studies have demonstrated that intrathecal clonidine in doses of 15-45μg provides significant prolongation of spinal anesthesia without major adverse effects [6]. The analgesic effect of clonidine is dose-dependent, but higher doses are associated with increased incidence of hypotension and sedation.

Nalbuphine, a mixed opioid agonist-antagonist, represents another promising adjuvant for spinal anesthesia. As a κ-receptor agonist and μ-receptor antagonist, nalbuphine provides analgesia with potentially fewer side effects compared to pure μ-agonists [7]. The drug's unique pharmacological profile theoretically reduces the risk of respiratory depression while maintaining analgesic efficacy. Intrathecal nalbuphine has been shown to prolong postoperative analgesia when combined with various local anesthetics [8].

The mechanisms of action of clonidine and nalbuphine differ significantly. While clonidine works through α2-adrenergic pathways, nalbuphine acts primarily through opioid receptors in the spinal cord. This difference in mechanism may translate into distinct clinical profiles regarding efficacy, duration of action, and side effects [9]. Understanding these differences is crucial for optimal selection of adjuvants based on patient characteristics and surgical requirements.

Despite individual studies on both adjuvants, direct comparative data between intrathecal clonidine and nalbuphine with ropivacaine are limited. Most existing studies have compared these adjuvants with bupivacaine or evaluated them against placebo [10]. The combination of hyperbaric ropivacaine with these adjuvants remains relatively unexplored, particularly in the context of orthopedic surgery where prolonged analgesia is highly desirable.

Orthopedic surgeries, especially those involving bones and joints, are associated with significant postoperative pain. Effective regional anesthesia not only provides intraoperative anesthetic conditions but also contributes to enhanced recovery through better pain control, early mobilization, and reduced opioid consumption [11]. The choice of adjuvant can significantly impact these outcomes.

This study aims to compare the efficacy and safety of intrathecal clonidine versus nalbuphine as adjuvants to hyperbaric ropivacaine in patients undergoing lower limb orthopedic surgery under subarachnoid block. We hypothesize that both adjuvants will enhance the quality and duration of spinal anesthesia compared to ropivacaine alone, with potential differences in their efficacy and side effect profiles.

Materials and Methods

Study Design and Ethical Considerations

This investigation employed a prospective, randomized, double-blind, placebo-controlled clinical trial design conducted at a tertiary care teaching hospital over an 11-month period from March 2023 to February 2024. The prospective nature ensured systematic data collection and minimized recall bias, while the randomized allocation eliminated selection bias and ensured comparable baseline characteristics across treatment groups.

The double-blind design was crucial for maintaining objectivity, as both patients and outcome assessors remained unaware of group allocation throughout the study period. This design feature prevented potential bias in subjective outcome measures such as pain scores and satisfaction ratings. The controlled nature of the trial, with ropivacaine alone serving as the active control group, provided a clinically relevant comparison rather than using an inactive placebo, which would have been ethically inappropriate in surgical patients requiring anesthesia.

Ethical approval was obtained from the Institutional Ethics Committee (IEC/2023/AN/045) following comprehensive review of the study protocol, risk-benefit analysis, and patient safety measures. The study was prospectively registered with the Clinical Trials Registry of India (CTRI/2023/03/050234) to ensure transparency and prevent selective reporting of outcomes. This registration occurred prior to patient enrollment, demonstrating commitment to research integrity and adherence to good clinical practice guidelines.

Written informed consent was obtained from all participants following detailed explanation of study procedures, potential risks and benefits, voluntary nature of participation, and right to withdraw at any time without affecting their clinical care. The consent process was conducted in the patient's preferred language by qualified investigators, ensuring full comprehension of study requirements.

The study strictly adhered to the Declaration of Helsinki principles, particularly regarding the ethical conduct of medical research involving human subjects. All procedures prioritized patient safety and welfare over research objectives. Additionally, the study followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines to ensure transparent and complete reporting of methodology and results, facilitating proper interpretation and potential replication of findings.

Subject Recruitment and Selection Criteria

Eligibility Requirements for Study Participation

The study population comprised adult patients aged 18-65 years presenting for elective lower limb orthopedic procedures under spinal anesthesia. This age range was selected to include physically active adults while excluding elderly patients who might have altered drug pharmacokinetics or increased comorbidity burden that could confound results. All participants were required to have

American Society of Anesthesiologists (ASA) physical status classification of I or II, ensuring the inclusion of healthy patients or those with mild systemic disease without functional limitations. This criterion was essential to minimize perioperative complications and ensure homogeneous baseline health status across groups.

The surgical scope was limited to elective lower limb orthopedic procedures with anticipated duration between 60-180 minutes. This timeframe was strategically chosen to allow adequate assessment of block characteristics while avoiding excessively long procedures that might introduce confounding variables related to surgical stress or positioning effects. Body Mass Index restrictions of 18.5-30 kg/m² were implemented to exclude underweight and obese patients, as extreme body habitus can significantly affect local anesthetic distribution in the subarachnoid space and potentially alter block dynamics. Similarly, height restrictions of 150-185 cm ensured relatively uniform cerebrospinal fluid volume and spinal anatomy, reducing variability in drug spread patterns.

Safety Considerations and Contraindication Criteria

Patient autonomy was paramount, with exclusion of any individual who refused participation or demonstrated inability to provide informed consent. This ethical consideration ensured voluntary participation and protected vulnerable populations who might not fully comprehend study implications. Standard contraindications to spinal anesthesia constituted absolute exclusion criteria, including patient refusal of the technique, infection at the puncture site, severe hypovolemia, increased intracranial pressure, or severe spinal deformity that would technically compromise the procedure.

Known allergies to any study medications, including ropivacaine, clonidine, or nalbuphine, necessitated exclusion to prevent potentially life-threatening hypersensitivity reactions. Cardiovascular exclusions focused on significant cardiac disease, particularly ejection fraction below 40%, as both clonidine and the sympathetic blockade from spinal anesthesia could precipitate hemodynamic instability in patients with compromised cardiac reserve. Uncontrolled hypertension and diabetes were excluded due to their potential to affect autonomic responses and complicate interpretation of hemodynamic outcomes.

Patients with chronic pain conditions or those receiving regular analgesic medications were excluded to prevent tolerance effects that might alter pain perception and duration of analgesia assessments. Pregnancy and lactation represented absolute contraindications due to unknown fetal effects of the study drugs and ethical considerations regarding research in pregnant women. Neurological disorders were excluded as they could interfere with accurate assessment of sensory and motor block characteristics, while hepatic or renal dysfunction might alter drug metabolism and clearance, potentially affecting both efficacy and safety outcomes. Finally, coagulation disorders posed risks for neuraxial hematoma formation, making spinal anesthesia contraindicated in these patients.

Sample Size Determination

Sample size was calculated based on a pilot study showing mean duration of sensory block of 170±25 minutes with ropivacaine alone. Assuming a 30% increase in duration as clinically significant, with α=0.05 and power of 80%, 27 patients per group were required. Accounting for 10% dropout, 30 patients per group were recruited.

Allocation Concealment and Methodological Masking Protocols

Computer-generated random number sequences in blocks of 9 were used for randomization. Allocation concealment was maintained using sealed, opaque envelopes opened immediately before the procedure. Study drugs were prepared by an anesthesiologist not involved in patient care or assessment. All syringes appeared identical, containing 3ml total volume. Patients, operating anesthesiologists, surgeons, and outcome assessors remained blinded throughout the study.

Treatment Stratification and Pharmaceutical Protocols

Therapeutic Group Allocation and Drug Administration Regimens

The study cohort was systematically stratified into three distinct treatment arms, each receiving standardized intrathecal drug combinations with identical total injection volumes to maintain blinding integrity. The control group, designated as Group R, received the baseline therapeutic regimen consisting of 2ml hyperbaric ropivacaine 0.75% containing 15mg of active compound, combined with 1ml normal saline as an inert diluent to achieve the standard 3ml total injection volume. This control arm served as the reference standard against which the efficacy of adjuvant medications could be objectively assessed.

The first experimental arm, Group RC (Ropivacaine-Clonidine), incorporated the α2-adrenergic agonist clonidine as a neuraxial adjuvant. Participants in this group received the identical baseline dose of 2ml hyperbaric ropivacaine 0.75% (15mg) supplemented with 30µg clonidine dissolved in 1ml sterile solution. This clonidine dosage was selected based on extensive literature review indicating optimal analgesic enhancement with minimal adverse effects within the 15-45µg range, while the 30µg dose represents the midpoint of this therapeutic window.

The second experimental cohort, Group RN (Ropivacaine-Nalbuphine), utilized the mixed opioid agonist-antagonist nalbuphine as the adjuvant compound. These subjects received the standard 2ml hyperbaric ropivacaine 0.75% (15mg) augmented with 0.8mg nalbuphine in 1ml carrier solution. The nalbuphine dose of 0.8mg was determined through systematic review of previous neuraxial studies demonstrating significant analgesic prolongation without excessive side effects, representing an optimal balance between therapeutic efficacy and safety profile for intrathecal administration.

Perioperative Management and Neuraxial Administration Protocol

All patients received standardized preoperative preparation. After overnight fasting, patients received oral ranitidine 150mg and metoclopramide 10mg two hours before surgery. In the operating room, standard monitoring included ECG, non-invasive blood pressure, pulse oximetry, and respiratory rate. Baseline vital signs were recorded.

Intravenous access was established with an 18G cannula, and preloading with 10-15ml/kg Ringer's lactate was performed. Under strict aseptic precautions, lumbar puncture was performed at L3-4 or L4-5 interspace using a 25G Quincke needle in sitting position. After confirming free flow of clear cerebrospinal fluid, the study drug was injected at a rate of

0.2ml/second. Patients were immediately made supine.

Assessment Methods

Sensory block was assessed using pinprick method with a 23G hypodermic needle every 2 minutes until maximum height was achieved, then every 15 minutes. Motor block was evaluated using Modified Bromage Scale (0=no block, 1=inability to raise extended leg, 2=inability to flex knee, 3=inability to flex ankle). Hemodynamic parameters were recorded every 3 minutes for first 15 minutes, then every 5 minutes throughout surgery.

Clinical Assessment Parameters and Evaluation Metrics

Principal Neuraxial Block Characteristics and Performance Indicators

The primary assessment focused on comprehensive evaluation of neuraxial blockade performance, beginning with precise measurement of sensory block onset kinetics defined as the temporal interval required to achieve complete sensory anesthesia at the T10 dermatome level. This specific anatomical landmark was selected as it represents the critical threshold for adequate anesthesia in lower limb orthopedic procedures, ensuring surgical readiness assessment. The maximum cephalad extent of sensory blockade was systematically documented to characterize the peak distribution of local anesthetic effect and determine the adequacy of surgical anesthesia coverage.

Duration of sensory blockade represented a crucial efficacy parameter, measured as the temporal interval from maximum block height until two-segment dermatomal regression occurred. This specific regression point was chosen as it indicates clinically meaningful reduction in anesthetic intensity while maintaining sufficient residual analgesia. Motor blockade assessment encompassed both onset characteristics, defined as time to achieve complete motor paralysis (Modified Bromage Scale grade 3), and duration parameters, measured until complete motor function recovery to baseline status.

Secondary Clinical Parameters and Safety Surveillance Metrics

Analgesic duration constituted a critical secondary parameter, quantified as the temporal interval from neuraxial injection until the patient's first spontaneous request for supplemental analgesia or documented Visual Analog Scale pain scores exceeding 4/10. This endpoint provided objective assessment of clinically meaningful analgesic cessation and practical relevance for postoperative pain management strategies.

Comprehensive hemodynamic surveillance included continuous monitoring of systolic and diastolic blood pressure parameters, heart rate variability, and detection of clinically significant cardiovascular perturbations. Pain intensity was systematically evaluated using standardized Visual Analog Scale methodology at predetermined temporal intervals, providing quantitative assessment of analgesic efficacy throughout the observation period. Sedation levels were objectively measured using the validated Ramsay Sedation Scale, ranging from anxious agitation to deep sedation, ensuring systematic evaluation of consciousness levels and patient comfort.

Safety surveillance encompassed systematic documentation of adverse physiological responses including hypotensive episodes (defined as >20% reduction from baseline or systolic pressure <90mmHg), bradycardic events (heart rate <50 beats per minute), gastrointestinal disturbances manifesting as nausea or vomiting, thermoregulatory dysfunction presenting as shivering, and dermatological reactions such as pruritus. Patient satisfaction was quantitatively assessed using a validated 5-point Likert scale methodology, providing standardized measurement of subjective treatment acceptability and overall perioperative experience quality.

Management of Complications

Hypotension (>20% decrease from baseline or systolic BP <90mmHg) was treated with intravenous ephedrine 6mg boluses. Bradycardia (heart rate <50bpm) was managed with atropine 0.6mg intravenously. Postoperative pain (VAS >4) was treated with intravenous tramadol 50mg.

Statistical Analysis

Data analysis was performed using SPSS version 26.0. Normality was assessed using Shapiro-Wilk test. Parametric data were expressed as mean±SD and analyzed using one-way ANOVA with post-hoc Tukey test. Non-parametric data were expressed as median (IQR) and analyzed using Kruskal-Wallis test. Categorical variables were analyzed using chi-square or Fisher's exact test. $P<0.05$ was considered statistically significant.

Results

Subject Enrollment Trajectory and Baseline Characteristics

Of 102 patients screened, 90 met inclusion criteria and completed the study protocol (Figure 1). There were no dropouts or protocol violations. Demographic characteristics and surgical parameters were comparable among groups (Table 1).

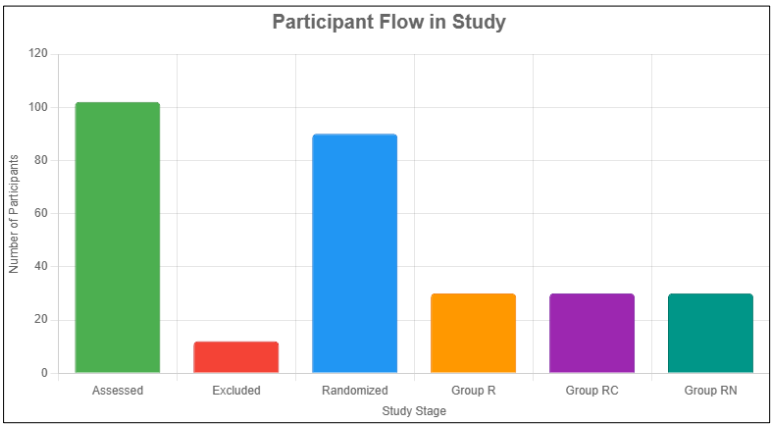

Fig 1: CONSORT Flow Diagram

Table 1: Demographic and Surgical Characteristics

Parameter	Group R (n=30)	Group RC (n=30)	Group RN (n=30)	P value
Age (years)	42.3±12.8	44.1±11.6	41.8±13.2	0.762
Sex (M/F)	18/12	20/10	19/11	0.819
Weight (kg)	68.4±9.2	69.8±8.7	67.9±9.5	0.698
Height (cm)	168.2±7.3	169.5±6.8	167.8±7.6	0.654
ASA I/II	16/14	18/12	17/13	0.875
Surgery duration (min)	92.4±18.6	94.8±20.2	91.6±19.4	0.804

Block Characteristics

Both adjuvant groups demonstrated significantly faster onset of sensory block compared to control. The highest sensory level achieved was comparable among groups, with median T6 level. However, duration of both sensory and motor block was significantly prolonged in adjuvant groups (Table 2, Figure 2).

Table 2: Block Characteristics

Parameter	Group R	Group RC	Group RN	P value
Sensory Block				
Onset to T10 (min)	5.8±1.1	4.2±0.8*	4.5±0.9*	<0.001
Maximum level (median)	T6 (T4-T8)	T6 (T4-T8)	T6 (T4-T8)	0.891
Time to max level (min)	12.3±2.4	10.8±2.1*	11.2±2.2	0.032
Duration (min)	168±21	246±28*†	218±24*	<0.001
Motor Block				
Onset to Bromage 3 (min)	8.9±1.7	6.8±1.4*	7.3±1.5*	<0.001
Duration (min)	142±17	198±22*†	176±19*	<0.001

*P<0.05 vs Group R, †P<0.05 vs Group RN

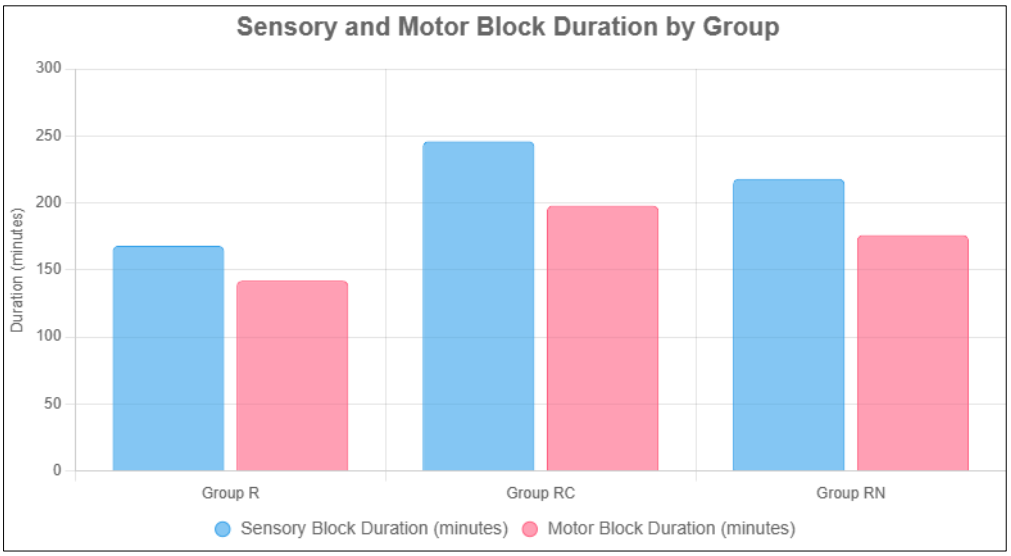

Fig 2: Duration of Sensory and Motor Block

Analgesic Profile

Time to first rescue analgesia was significantly prolonged in both adjuvant groups, with Group RC showing the longest duration. VAS scores remained lower in adjuvant groups throughout the observation period (Table 3).

Table 3: Analgesic Parameters and VAS Scores

Parameter	Group R	Group RC	Group RN	P value
Time to rescue analgesia (min)	246±31	386±42*†	342±38*	<0.001
VAS Scores				
2 hours	0.8±0.6	0.3±0.5*	0.4±0.5*	0.002
4 hours	2.4±0.8	1.2±0.7*	1.5±0.8*	<0.001
6 hours	3.8±1.0	2.1±0.9*	2.6±1.0*	<0.001
8 hours	4.6±1.2	3.2±1.1*	3.6±1.2*	<0.001

*P<0.05 vs Group R, †P<0.05 vs Group RN

Hemodynamic Changes and Adverse Effects

Group RC showed more pronounced hypotension requiring vasopressor support. Sedation scores were higher in Group RC. Other adverse effects were comparable among groups (Figure 3).

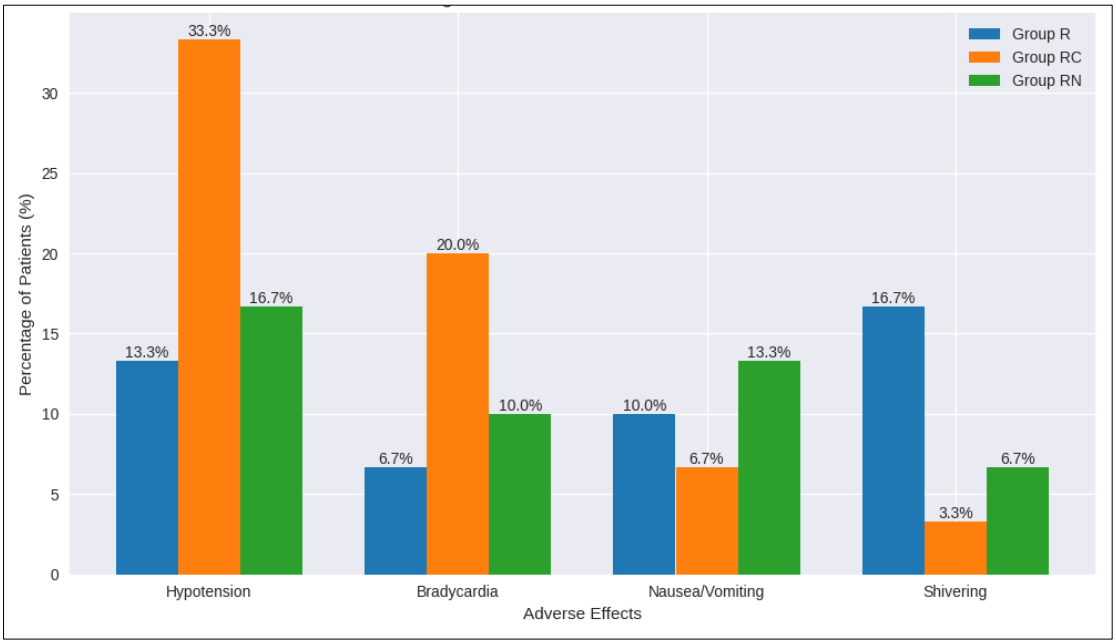

Fig 3: Incidence of Adverse Effects

Patient Satisfaction

Patient satisfaction scores were significantly higher in both adjuvant groups compared to control (RC: 4.6±0.5, RN: 4.4±0.6 vs R: 3.8±0.7; $p<0.001$).

Discussion

This study demonstrates that both clonidine and nalbuphine as intrathecal adjuvants significantly enhance the quality and duration of hyperbaric ropivacaine spinal anesthesia. The key findings include faster onset, prolonged duration of sensory and motor block, and extended postoperative analgesia with both adjuvants, though with distinct efficacy and safety profiles.

The faster onset of sensory block observed with both adjuvants can be attributed to their synergistic effects with ropivacaine. Clonidine, through its action on α2-adrenergic receptors, enhances local anesthetic action by inhibiting C-fiber conduction and facilitating local anesthetic binding [12]. Nalbuphine may facilitate neural blockade through modulation of calcium channels and enhancement of local anesthetic potency [13]. The clinical significance of this 1.3-1.6 minute reduction in onset time may be particularly relevant in emergency situations or high-turnover surgical settings.

The prolongation of sensory block duration represents one of the most clinically significant findings. Group RC showed a 46% increase (246 vs 168 minutes), while Group RN demonstrated a 30% increase (218 vs 168 minutes) compared to control. This prolongation aligns with previous studies on clonidine with other local anesthetics, though specific data with ropivacaine have been limited [14]. The superior performance of clonidine may relate to its direct action on substantia gelatinosa neurons and inhibition of substance P release, providing more profound neural blockade.

The differential effects on motor block duration merit careful consideration. While prolonged motor block may be advantageous during surgery, excessive prolongation can delay mobilization and discharge. Clonidine produced more prolonged motor block (198 minutes) compared to nalbuphine (176 minutes), which could influence adjuvant selection based on surgical requirements and institutional protocols for early ambulation.

The extended duration of analgesia with both adjuvants has important implications for postoperative pain management. The mean time to first rescue analgesia was extended by 57% with clonidine and 39% with nalbuphine. This prolongation can reduce overall opioid consumption, potentially minimizing opioid-related adverse effects and improving patient satisfaction [15]. The mechanisms underlying this prolonged analgesia differ between adjuvants - clonidine through spinal α2-receptor activation and nalbuphine through κ-opioid receptor agonism with minimal μ-receptor activity.

Hemodynamic effects represent a crucial safety consideration. The higher incidence of hypotension with clonidine (33.3% vs 16.7% with nalbuphine) reflects its sympatholytic properties. This finding is consistent with dose-dependent cardiovascular effects of neuraxial clonidine reported in meta-analyses [16]. While manageable with vasopressors, this increased hypotension risk may limit clonidine use in patients with compromised cardiovascular reserve or where fluid restriction is necessary.

The sedation observed with clonidine, while mild and not requiring intervention, represents another differentiating factor. This sedative effect, mediated through supraspinal α2-receptors, may be beneficial in anxious patients but could interfere with early neurological assessment in certain surgical contexts. Nalbuphine produced minimal sedation, consistent with its limited central nervous system penetration.

The lower incidence of shivering in both adjuvant groups is noteworthy. Clonidine's anti-shivering effect through reduction of shivering threshold and nalbuphine's action on multiple receptor systems both contribute to improved patient comfort. This effect is particularly valuable given that shivering increases oxygen consumption and can compromise surgical outcomes in patients with limited cardiopulmonary reserve.

Our findings support the concept of multimodal spinal anesthesia, where adjuvants targeting different mechanisms can optimize block characteristics while potentially reducing individual drug doses and associated side effects. The choice between clonidine and nalbuphine should be individualized based on patient factors, surgical requirements, and

institutional preferences. Clonidine may be preferred when maximum block duration is desired and hemodynamic stability can be maintained. Nalbuphine offers a favorable alternative when cardiovascular stability is paramount or in patients prone to excessive sedation.

Study limitations include the single-center design, fixed dosing regimen, and relatively short follow-up period. We did not evaluate different dose combinations or assess long-term outcomes such as persistent neurological symptoms or chronic pain. The study population excluded elderly patients and those with significant comorbidities, potentially limiting generalizability. Future research should explore dose-response relationships, combination therapy with both adjuvants at lower doses, and applicability in high-risk populations [17].

Conclusion

Both intrathecal clonidine (30µg) and nalbuphine (0.8mg) effectively enhance hyperbaric ropivacaine spinal anesthesia for lower limb orthopedic surgery. Clonidine provides superior block characteristics with longer sensory and motor block duration and more prolonged analgesia. However, this comes at the cost of increased hypotension and sedation. Nalbuphine offers a balanced profile with significant block enhancement but better hemodynamic stability. The choice of adjuvant should be individualized based on patient characteristics, surgical requirements, and the need to balance efficacy against potential adverse effects. These findings support the routine use of intrathecal adjuvants to optimize spinal anesthesia outcomes in orthopedic surgery.

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