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A COMPARATIVE STUDY OF EPIDURAL PLAIN NALBUPHINE VERSUS TRAMADOL FOR POSTOPERATIVE ANALGESIA IN LOWER LIMB SURGERIES

Anaesthesiology

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ABSTRACT

Background Effective postoperative analgesia is crucial for patient comfort and recovery following lower limb surgeries. Epidural opioids provide superior analgesia compared to systemic routes. Nalbuphine and tramadol have distinct pharmacological profiles that may influence their analgesic efficacy when used epidurally.**Objective** To compare the efficacy and safety of epidural plain nalbuphine (10 mg) versus epidural plain tramadol (50 mg) for postoperative analgesia in patients undergoing lower limb surgery. **Methods** This prospective, randomized, double-blind study included 60 ASA I–II patients undergoing elective lower limb surgeries under combined spinal–epidural anaesthesia. Patients were randomized into two groups: Group N (n=30) receiving epidural nalbuphine 10 mg diluted to 10 mL, and Group T (n=30) receiving epidural tramadol 50 mg diluted to 10 mL. Primary outcome was duration of postoperative analgesia. Secondary outcomes included Visual Analogue Scale (VAS) scores, hemodynamic parameters, and adverse effects.**Results** Group N demonstrated significantly longer duration of analgesia compared to Group T (14.8 ± 2.3 vs 9.4 ± 1.8 hours; $p < 0.001$). VAS scores were significantly lower in Group N at 6, 8, 12, and 16 hours postoperatively ($p < 0.05$). Hemodynamic parameters remained comparable between groups. Nausea and vomiting were more common in Group T (40% vs 16.7%; $p < 0.05$), while mild sedation was more frequent in Group N (33.3% vs 13.3%; $p < 0.05$). No respiratory depression occurred in either group. **Conclusion** Epidural nalbuphine 10 mg provides superior and prolonged postoperative analgesia with a favorable safety profile compared to epidural tramadol 50 mg in lower limb surgeries. Nalbuphine offers a longer analgesic duration with lower incidence of nausea and vomiting, making it an effective alternative for postoperative pain management.

KEYWORDS

Epidural Analgesia; Nalbuphine; Tramadol; Postoperative Pain; Lower Limb Surgery; Opioid Agonist-antagonist

INTRODUCTION

Postoperative pain management is a critical component of perioperative care that significantly influences patient outcomes, recovery time, and satisfaction. Inadequately controlled postoperative pain can lead to numerous complications including delayed mobilization, increased risk of thromboembolic events, pulmonary complications, chronic pain syndromes, and prolonged hospital stay [1,2]. Lower limb surgeries, which include procedures on the hip, knee, ankle, and foot, are associated with moderate to severe postoperative pain that can significantly impede rehabilitation and functional recovery [3].

Epidural analgesia has evolved as the gold standard for postoperative pain management following major lower limb surgeries. It provides superior analgesia compared to systemic opioids, reduces the neuroendocrine stress response to surgery, improves pulmonary function, reduces the incidence of deep vein thrombosis, and facilitates early mobilization [4,5]. The addition of opioids to the epidural space enhances the quality and duration of analgesia while allowing for reduced doses of local anesthetics, thereby minimizing hemodynamic side effects [6].

Nalbuphine hydrochloride is a synthetic opioid with mixed agonist-antagonist properties. It acts as a κ-receptor agonist and μ-receptor antagonist, providing effective analgesia with a ceiling effect on respiratory depression [7]. This unique pharmacological profile makes nalbuphine an attractive option for postoperative analgesia, particularly in the epidural space where it can provide prolonged pain relief with minimal systemic side effects [8]. Studies have demonstrated that nalbuphine provides effective analgesia with stable hemodynamics and a favorable safety profile [9,10].

Tramadol is a centrally acting synthetic opioid analgesic with a dual mechanism of action. It exhibits weak μ-opioid receptor agonist activity and also inhibits the reuptake of norepinephrine and serotonin in the central nervous system [11]. This monoaminergic activity contributes significantly to its overall analgesic effect and may enhance descending inhibitory pathways at the spinal level [12]. Tramadol has gained widespread acceptance for moderate to severe pain management and has been utilized in various regional anesthesia techniques [13].

While both nalbuphine and tramadol have been individually studied as epidural adjuvants, direct comparative studies evaluating their efficacy as plain epidural agents specifically for postoperative analgesia in lower limb surgeries remain limited. The different receptor profiles and mechanisms of action of these two agents suggest potentially different clinical effects in terms of analgesic efficacy, duration of action, and adverse effect profiles [14,15].

This study was designed to comprehensively compare the efficacy and safety of epidural plain nalbuphine 10 mg versus epidural plain tramadol 50 mg for postoperative analgesia in patients undergoing lower limb surgeries. The primary objective was to evaluate the duration of postoperative analgesia, while secondary objectives included assessment of pain intensity, hemodynamic stability, and incidence of adverse effects.

MATERIALS AND METHODS

Study Design and Setting

This prospective, randomized, double-blind, comparative study was conducted in the Department of Anaesthesiology at a tertiary care teaching hospital over 18 months. The study was approved by the Institutional Ethics Committee and registered with the Clinical Trials Registry. Written informed consent was obtained from all patients after explaining the study protocol, potential risks, and benefits in their preferred language.

Sample Size and Randomization

Based on previous studies and considering a power of 80% and alpha error of 5%, the minimum required sample size was calculated to be 25 patients per group [16]. To account for potential dropouts, 30 patients were included in each group, for a total of 60 patients. Patients were randomized into two groups using a computer-generated random number sequence concealed in sealed opaque envelopes.

Eligibility Criteria

Inclusion criteria comprised adult patients aged 18-65 years, American Society of Anesthesiologists (ASA) physical status I and II, scheduled for elective lower limb surgery under combined spinal-epidural anaesthesia, and with expected surgical duration of 1-3 hours.

Exclusion criteria included patient refusal, contraindications to neuraxial blockade (bleeding disorders, local infection, increased intracranial pressure), known allergy to study drugs or local anesthetics, chronic pain conditions or opioid dependence, significant

cardiovascular, respiratory, hepatic or renal disease, pregnancy or lactation, body mass index (BMI) > 35 kg/m², and psychiatric disorders or communication barriers.

Anesthetic Technique

All patients underwent standard preoperative evaluation and were kept nil per oral for 6 hours for solids and 2 hours for clear liquids. On arrival in the operating room, standard monitoring including electrocardiography, non-invasive blood pressure, and pulse oximetry was established. After securing an 18-gauge intravenous cannula, crystalloid preloading was initiated.

Combined spinal-epidural (CSE) anaesthesia was performed in the sitting position under strict aseptic precautions at the L3-L4 or L4-L5 interspace using the midline approach. After infiltration with 2% lignocaine, an 18-gauge Tuohy needle was inserted into the epidural space using the loss of resistance to saline technique. A 27-gauge Quincke spinal needle was inserted through the Tuohy needle into the subarachnoid space, and 3 mL of 0.5% hyperbaric bupivacaine was injected intrathecally after confirming free flow of cerebrospinal fluid [17].

Following withdrawal of the spinal needle, an epidural catheter was threaded 4-5 cm into the epidural space through the Tuohy needle. After negative aspiration for blood or cerebrospinal fluid, the catheter was secured. Sensory level was assessed using loss of pinprick sensation, and motor blockade was assessed using the modified Bromage scale [18].

Study Drug Preparation and Administration

At the completion of surgery, the study drug was administered through the epidural catheter. The drugs were prepared by an anesthesiologist not involved in patient care or data collection, ensuring double-blind conditions:

- Group N (Nalbuphine): Nalbuphine 10 mg (1 mL) was diluted with normal saline to a total volume of 10 mL, resulting in a concentration of 1 mg/mL.Group T (Tramadol): Tramadol 50 mg (1 mL) was diluted with normal saline to a total volume of 10 mL, resulting in a concentration of 5 mg/mL.

The prepared study solution was administered slowly over 5 minutes through the epidural catheter with continuous monitoring of heart rate, blood pressure, respiratory rate, and oxygen saturation. Both solutions appeared identical, maintaining blinding of patients and assessors.

Outcome Measures and Data Collection

The primary outcome measure was duration of postoperative analgesia, defined as the time from epidural drug administration to the first request for rescue analgesia (VAS ≥ 4). Secondary outcome measures included pain intensity assessed using the Visual Analogue Scale (VAS) at 0, 2, 4, 6, 8, 12, 16, 20, and 24 hours postoperatively, where 0 represented no pain and 10 represented worst imaginable pain [19].

Hemodynamic parameters including heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, respiratory rate, and oxygen saturation were recorded at the same time intervals. Sedation was assessed using the Ramsay Sedation Scale (1 = anxious and agitated; 2 = cooperative, oriented, tranquil; 3 = responds to commands only; 4 = brisk response to light glabellar tap; 5 = sluggish response to stimulus; 6 = no response) [20].

Adverse effects including nausea, vomiting, pruritus, respiratory depression (respiratory rate < 8 breaths/min), urinary retention, and excessive sedation were recorded. Total rescue analgesic consumption in 24 hours and patient satisfaction score (1 = poor, 2 = fair, 3 = good, 4 = excellent) at 24 hours were also documented.

Rescue Analgesia and Adverse Effect Management

When VAS score was ≥ 4 or when the patient requested additional analgesia, rescue analgesia was provided with intravenous paracetamol 1 gram. If pain persisted after 30 minutes, intramuscular diclofenac 75 mg was administered. Nausea and vomiting were treated with intravenous ondansetron 4 mg. Respiratory depression was managed with supplemental oxygen, assisted ventilation if needed, and naloxone if severe [21].

Statistical Analysis

Data were analyzed using SPSS software version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) and compared using independent t-test. Categorical variables were expressed as frequencies and percentages and compared using chi-square test or Fisher's exact test as appropriate. VAS scores and hemodynamic parameters at different time points were analyzed using repeated measures ANOVA. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 60 patients were enrolled and randomized into two groups of 30 patients each. All patients completed the study protocol with no dropouts or protocol violations.

Demographic and Clinical Characteristics

The demographic and clinical characteristics were comparable between the two groups (Table 1). There were no statistically significant differences in age, gender distribution, body weight, height, BMI, ASA physical status, type of surgery, or duration of surgery (p > 0.05 for all comparisons).

Table 1: Demographic and Clinical Characteristics of Study Participants

Parameter	Group N (n=30)	Group T (n=30)
Age (years)	42.3 ± 11.2	43.7 ± 10.8
Gender (Male/Female)	18/12	17/13
Weight (kg)	64.5 ± 8.3	65.8 ± 9.1
BMI (kg/m²)	24.2 ± 2.8	24.6 ± 3.1
ASA Status (I/II)	20/10	19/11
Duration of surgery (minutes)	98.5 ± 22.4	102.3 ± 24.1

Data presented as mean ± SD or number of patients. BMI: body mass index; ASA: American Society of Anesthesiologists. No significant differences between groups (p > 0.05).

Primary Outcome: Duration of Analgesia

The mean duration of postoperative analgesia in Group N was significantly longer compared to Group T (14.8 ± 2.3 hours vs 9.4 ± 1.8 hours; p < 0.001), representing approximately 57% longer duration with epidural nalbuphine (Table 2). The time to first request for rescue analgesia showed similar results, with Group N demonstrating a significantly prolonged analgesic effect.

Table 2: Duration of Analgesia and Rescue Analgesic Requirements

Parameter	Group N (n=30)	Group T (n=30)
Duration of analgesia (hours)	14.8 ± 2.3*	9.4 ± 1.8
Time to first rescue (hours)	14.8 ± 2.3*	9.4 ± 1.8
Total rescue doses in 24 hours	1.2 ± 0.5*	2.1 ± 0.7

Data presented as mean ± SD. * p < 0.001 compared to Group T.

Visual Analogue Scale Scores

VAS scores were significantly lower in Group N compared to Group T at 6, 8, 12, and 16 hours postoperatively (p < 0.05 for all comparisons, Table 3). Both groups had comparable VAS scores at 0, 2, and 4 hours. At 20 and 24 hours, most patients in both groups had requested rescue analgesia, resulting in non-significant differences in VAS scores.

Table 3: Visual Analogue Scale (VAS) Scores at Different Time Intervals

Adverse Effect	Group N n (%)	Group T n (%)
Nausea and vomiting	5 (16.7%)*	12 (40.0%)
Mild sedation (Ramsay 3)	10 (33.3%)*	4 (13.3%)
Pruritus	3 (10.0%)	2 (6.7%)
Respiratory depression	0 (0%)	0 (0%)
Urinary retention	1 (3.3%)	1 (3.3%)

*Data presented as mean ± SD. VAS: Visual Analogue Scale (0 = no pain, 10 = worst pain). *p < 0.05 compared to Group T.*

Hemodynamic Parameters

Hemodynamic parameters including heart rate, systolic and diastolic blood pressure, mean arterial pressure, respiratory rate, and oxygen saturation remained stable and comparable between the two groups throughout the 24-hour observation period (p > 0.05 for all comparisons at all time points). No clinically significant hemodynamic

instability was observed in either group. There were no episodes of bradycardia, hypotension, or desaturation requiring intervention.

Adverse Effects

The incidence of adverse effects is summarized in Table 4. Nausea and vomiting were significantly more common in Group T compared to Group N (40% vs 16.7%; $p < 0.05$). Mild sedation (Ramsay score 3) was more frequent in Group N (33.3% vs 13.3%; $p < 0.05$), but all patients remained easily arousable and no intervention was required. Pruritus occurred in 10% of patients in Group N and 6.7% in Group T ($p > 0.05$). No patient in either group experienced respiratory depression (respiratory rate < 8 breaths/min or $SpO_2 < 90\%$). Urinary retention occurred in one patient in each group, both requiring catheterization.

Table 4: Incidence of Adverse Effects

Time (hours)	Group N (n=30)	Group T (n=30)
0	0.8 ± 0.4	0.9 ± 0.5
2	1.2 ± 0.6	1.3 ± 0.7
4	1.8 ± 0.8	2.1 ± 0.9
6	2.3 ± 1.0*	3.2 ± 1.1
8	2.9 ± 1.2*	4.1 ± 1.3
12	3.4 ± 1.3*	4.8 ± 1.4

*Data presented as number (percentage). * $p < 0.05$ compared to Group T.*

Patient Satisfaction

Patient satisfaction scores at 24 hours were significantly higher in Group N compared to Group T. In Group N, 20 patients (66.7%) rated their pain management as excellent, 8 (26.7%) as good, and 2 (6.7%) as fair. In Group T, 10 patients (33.3%) rated it as excellent, 13 (43.3%) as good, 6 (20.0%) as fair, and 1 (3.3%) as poor ($p < 0.05$).

DISCUSSION

This randomized, double-blind study compared the efficacy and safety of epidural plain nalbuphine 10 mg versus epidural plain tramadol 50 mg for postoperative analgesia in patients undergoing lower limb surgeries. Our findings demonstrate that epidural nalbuphine provides significantly superior analgesia with a longer duration of action and a more favorable adverse effect profile compared to tramadol.

Duration of Analgesia

The primary finding of this study was that epidural nalbuphine provided significantly longer duration of postoperative analgesia (14.8 ± 2.3 hours) compared to tramadol (9.4 ± 1.8 hours). This represents approximately 57% longer analgesic duration with nalbuphine, which has important clinical implications for postoperative pain management. The extended duration of analgesia reduces the need for frequent analgesic interventions and potentially improves patient comfort and satisfaction.

These findings are consistent with previous studies evaluating nalbuphine in the epidural space. Kumar et al. reported that epidural nalbuphine 10 mg provided effective analgesia for 12-16 hours following abdominal surgeries [15]. The longer duration observed in our study may be attributed to the specific patient population and surgical type. The mechanism underlying the prolonged action of epidural nalbuphine involves its high affinity for κ-opioid receptors, which are abundantly distributed in the dorsal horn of the spinal cord [22].

The shorter duration of analgesia with tramadol in our study is comparable to findings by Baraka et al., who reported epidural tramadol 50 mg provided analgesia for 8-10 hours [19]. Tramadol's dual mechanism of action (weak μ-opioid agonism and monoaminergic effects) may provide adequate analgesia, but its relatively weak opioid receptor affinity may limit its duration of action when used as a sole epidural agent [23].

Pain Intensity and Rescue Analgesia

VAS scores were significantly lower in the nalbuphine group at 6, 8, 12, and 16 hours postoperatively, indicating superior pain control during this critical period. This corresponds with the peak analgesic effect of epidural opioids and reflects the different receptor pharmacodynamics of the two agents. The κ-agonist activity of nalbuphine appears to provide more effective spinal analgesia for somatic pain associated with lower limb surgeries [24].

The significantly lower rescue analgesic requirement in Group N (1.2 ± 0.5 doses) compared to Group T (2.1 ± 0.7 doses) further supports the superior analgesic efficacy of epidural nalbuphine. Reduced rescue analgesic consumption translates to decreased exposure to additional medications and their potential side effects, which is particularly relevant in the context of multimodal analgesia and enhanced recovery protocols [25].

Hemodynamic Stability

Both groups demonstrated comparable hemodynamic stability throughout the study period, with no clinically significant differences in heart rate, blood pressure, respiratory rate, or oxygen saturation. This finding is consistent with the known pharmacological profiles of both drugs when administered epidurally. Unlike local anesthetics, epidural opioids do not cause sympathetic blockade and thus maintain hemodynamic stability [26].

The hemodynamic stability observed in both groups suggests that either agent can be safely used in patients with mild cardiovascular disease (ASA II), provided appropriate monitoring is maintained. This is particularly important in the context of lower limb surgeries, which are frequently performed in elderly patients with comorbidities [27].

Adverse Effect Profile

The adverse effect profile represents an important differentiating factor between the two study drugs. Nausea and vomiting were significantly more common in the tramadol group (40% vs 16.7%). This finding is consistent with tramadol's known serotonergic effects, which contribute to increased chemoreceptor trigger zone activation [28]. The higher incidence of postoperative nausea and vomiting (PONV) with tramadol may necessitate prophylactic antiemetic administration, adding complexity to the analgesic regimen.

Conversely, mild sedation was more common in the nalbuphine group (33.3% vs 13.3%). This is attributable to nalbuphine's κ-agonist activity, which has known sedative properties [29]. However, it is important to note that all instances of sedation in our study were mild (Ramsay score 3 or less), with patients remaining easily arousable and requiring no intervention. In the postoperative setting, mild sedation may actually be beneficial for patient comfort and anxiety reduction, particularly during the immediate postoperative period.

Critically, no patient in either group experienced respiratory depression, defined as respiratory rate less than 8 breaths/min or oxygen saturation below 90%. This finding supports the excellent safety profile of both drugs when used at these doses for epidural administration. Nalbuphine's ceiling effect on respiratory depression, mediated by its μ-receptor antagonist activity, provides an additional margin of safety [30]. While tramadol is a weak μ-agonist and carries lower risk of respiratory depression compared to traditional opioids, the doses used in epidural administration are generally safe with appropriate monitoring [31].

Patient Satisfaction

Patient satisfaction was significantly higher in the nalbuphine group, with 66.7% of patients rating their pain management as excellent compared to 33.3% in the tramadol group. This difference likely reflects the combined impact of superior analgesia, longer duration of action, and lower incidence of distressing side effects such as nausea and vomiting. Patient satisfaction is increasingly recognized as an important outcome measure in perioperative care and is associated with better overall recovery experiences [32].

Clinical Implications

The findings of this study have several important clinical implications. First, epidural nalbuphine appears to be an excellent choice for postoperative analgesia in lower limb surgeries, providing prolonged pain relief with minimal side effects. The extended duration of analgesia may reduce the need for frequent analgesic interventions, potentially decreasing healthcare worker burden and improving patient comfort.

Second, the lower incidence of nausea and vomiting with nalbuphine is clinically significant, as PONV is one of the most distressing postoperative complications and can delay discharge and increase healthcare costs [33]. The use of nalbuphine may reduce the need for prophylactic or therapeutic antiemetics, simplifying the postoperative medication regimen.

Third, the excellent safety profile of nalbuphine, particularly regarding respiratory depression, makes it an attractive option even in patients who may be at higher risk for opioid-related respiratory complications. The ceiling effect on respiratory depression provides an inherent safety mechanism that may be particularly valuable in resource-limited settings where intensive monitoring may not be available.

Limitations

This study has several limitations that should be acknowledged. First, the sample size, while adequate for detecting differences in primary outcomes, may have been insufficient to detect rare but serious adverse events. Larger multicenter studies would be valuable to further characterize the safety profile of these agents.

Second, the study was conducted at a single center, which may limit the generalizability of findings to different patient populations or practice settings. Third, we did not evaluate long-term outcomes such as chronic postsurgical pain or functional recovery, which would provide additional valuable information about the clinical impact of different analgesic strategies.

Fourth, we used fixed doses of both drugs based on previous literature rather than weight-based dosing. While this approach is consistent with common clinical practice for epidural opioids, future studies could explore dose-response relationships to optimize analgesic efficacy while minimizing side effects. Finally, we did not evaluate these agents in combination with local anesthetics, which is a common clinical practice that may influence both efficacy and safety profiles.

Future Directions

Future research should focus on several areas to build upon these findings. Comparative studies evaluating different doses of epidural nalbuphine could help identify the optimal dose that maximizes analgesia while minimizing side effects. Studies comparing epidural nalbuphine with other commonly used epidural opioids such as morphine or fentanyl would provide additional context for clinical decision-making.

Investigations into combinations of epidural nalbuphine with local anesthetics or other adjuvants could identify synergistic effects that further improve analgesia. Cost-effectiveness analyses comparing different epidural analgesic strategies would help healthcare systems make informed decisions about resource allocation. Finally, studies evaluating the impact of epidural nalbuphine on rehabilitation outcomes and time to functional recovery would provide valuable information about the overall value of this approach to pain management.

CONCLUSION

This prospective, randomized, double-blind study demonstrates that epidural plain nalbuphine 10 mg provides superior postoperative analgesia compared to epidural plain tramadol 50 mg in patients undergoing lower limb surgeries. Nalbuphine offers significantly longer duration of analgesia, better pain control as evidenced by lower VAS scores, reduced requirement for rescue analgesia, and higher patient satisfaction. The adverse effect profile of nalbuphine is favorable, with significantly lower incidence of nausea and vomiting compared to tramadol. While mild sedation was more common with nalbuphine, it was clinically insignificant and required no intervention. Importantly, neither agent caused respiratory depression, confirming their excellent safety profile.

Based on these findings, epidural nalbuphine 10 mg can be recommended as an effective and safe option for postoperative analgesia in lower limb surgeries, offering advantages over tramadol in terms of analgesic efficacy, duration of action, and side effect profile. The unique pharmacological properties of nalbuphine, particularly its κ-agonist and μ-antagonist activities resulting in a ceiling effect on respiratory depression, make it an attractive choice for postoperative pain management. Further research is warranted to explore optimal dosing strategies, combinations with other analgesics, and long-term functional outcomes associated with this approach.

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Ethical Approval: The study was approved by the Institutional Ethics Committee and registered with the Clinical Trials Registry. All participants provided written informed consent.

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