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Original Research Article

Comparative Evaluation of Postoperative Analgesia Following Intrathecal Hyperbaric Bupivacaine with Fentanyl versus Nalbuphine for Lower Limb Surgery

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Abstract

Background and Objectives: Prolongation of postoperative analgesia remains an important objective of spinal anaesthesia, particularly following lower limb surgery, where early mobilisation and effective pain control are essential for functional recovery. Fentanyl is a commonly used lipophilic opioid adjuvant, whereas nalbuphine, a mixed opioid agonist-antagonist with predominant κ-receptor agonist activity and μ-receptor antagonistic properties, has emerged as a potential alternative.

Methods: A randomized prospective comparative study was conducted in 60 patients aged 20–55 years with American Society of Anesthesiologists (ASA) physical status I or II undergoing lower limb surgery under spinal anaesthesia. Patients were randomized into two equal groups of 30 each. Group BUF received 15 mg of 0.5% hyperbaric bupivacaine with fentanyl 25 μg intrathecally, whereas Group BUN received 15 mg of 0.5% hyperbaric bupivacaine with nalbuphine 1 mg intrathecally. The primary outcome was the interval from intrathecal drug administration to the first request for postoperative rescue analgesia.

Results: The mean time to first rescue analgesia was significantly longer in Group BUN than in Group BUF (686.50±129.37 versus 379.50±54.11 minutes; $p<0.001$). The absolute between-group difference was 307 minutes, corresponding to approximately 5.1 additional hours of analgesia with nalbuphine. The derived 95% confidence interval for the mean difference was approximately 255.2–358.8 minutes. The standardized effect size was large (Cohen's $d\approx3.10$). Mean motor block duration was comparable between the groups, measuring 168.83±9.71 minutes in Group BUF and 170.83±9.48 minutes in Group BUN.

Conclusion: Addition of 1 mg intrathecal nalbuphine to 15 mg hyperbaric bupivacaine produced a significantly longer duration of postoperative analgesia than 25 μg intrathecal fentanyl. The prolongation of analgesia occurred without meaningful prolongation of motor blockade, suggesting that nalbuphine may be an effective intrathecal adjuvant for extending postoperative pain relief following lower limb surgery.

Keywords: Nalbuphine; Fentanyl; Bupivacaine; Spinal Anaesthesia; Intrathecal Opioid; Postoperative Analgesia; Lower Limb Surgery.

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Introduction

Postoperative pain is an important determinant of recovery following lower limb surgery. Inadequately controlled acute postoperative pain may interfere with mobilisation, sleep, physiotherapy, respiratory function and patient satisfaction and may contribute to prolonged hospitalisation.[1] Although spinal anaesthesia provides excellent intraoperative analgesia, the analgesic effect of intrathecal local anaesthetics is limited by the duration of sensory blockade. Once the block regresses, patients may experience significant surgical-site pain and require systemic rescue analgesics.[2] The addition of intrathecal adjuvants to local anaesthetics is an established approach for improving the quality and duration of spinal anaesthesia. Intrathecal opioids produce analgesia through activation of opioid receptors in the spinal cord and can act synergistically with local anaesthetics. Fentanyl is frequently used because of its high lipid solubility, rapid onset and predictable spinal analgesic effects. However, opioid-related adverse effects such as nausea, vomiting, pruritus, sedation and respiratory depression remain important considerations.[3] Nalbuphine is a semisynthetic opioid with predominant κ-receptor agonist and μ-receptor

antagonist activity. Its pharmacological profile has generated interest in its use as an intrathecal adjuvant because it may enhance spinal analgesia while potentially producing fewer μ-opioid-related adverse effects. Several clinical studies have evaluated nalbuphine in combination with hyperbaric bupivacaine, including studies specifically involving lower limb orthopaedic surgery. [4]

Naaz et al. compared fentanyl with two doses of nalbuphine in patients undergoing lower limb orthopaedic surgery and reported significant differences in the duration and quality of postoperative analgesia. [1] More recent randomized studies have also demonstrated prolonged effective analgesia with intrathecal nalbuphine compared with fentanyl. One study involving 100 patients reported a mean duration of effective analgesia of 388±24.88 minutes with nalbuphine compared with 304.70±15.76 minutes with fentanyl. [5]

The present analysis focuses specifically on the clinically important endpoint of time to first postoperative rescue analgesia in a randomized study comparing 1 mg nalbuphine with 25 μg fentanyl, both combined with 15 mg hyperbaric bupivacaine.

Materials and Methods

Study design and setting: This randomized prospective comparative study was conducted in the Department of Anaesthesiology, Thumbay Hospital New Life, Hyderabad, over a period of six months.

Study Population: Sixty patients aged 20–55 years belonging to ASA physical status I or II and scheduled for lower limb surgery under spinal anaesthesia were included.

Patients with significant systemic comorbidities, contraindications to spinal anaesthesia, coagulation abnormalities, known hypersensitivity to study drugs, local infection/sepsis at the injection site and other conditions precluding spinal anaesthesia were excluded.

Randomization and study groups: Patients were randomly allocated using a sealed-envelope technique into two groups of 30 patients each.

Group BUF: 15 mg of 0.5% hyperbaric bupivacaine + fentanyl 25 μg intrathecally.

Group BUN: 15 mg of 0.5% hyperbaric bupivacaine + nalbuphine 1 mg intrathecally.

The study drugs were administered intrathecally under standard aseptic precautions following identification of the appropriate intervertebral space.

Postoperative Assessment: Following surgery, patients were observed in the post-anaesthesia/recovery area until adequate recovery of sensory and motor blockade. Postoperative vital parameters were monitored at regular intervals.

The primary endpoint was time from intrathecal drug administration to the patient's first request for rescue analgesia. Rescue analgesia was administered when the patient complained of pain at the operative site and consisted of either paracetamol 1 g or diclofenac 75 mg, according to the clinical requirement. Motor block duration was also documented.

Statistical Analysis: Continuous variables were summarized using mean and standard deviation. The primary outcome was compared between groups. A p value <0.05 was considered statistically significant.

For the expanded analysis, the between-group mean difference and approximate 95% confidence interval were calculated from the reported group means, standard deviations and sample sizes. Cohen's d was calculated as an estimate of standardized treatment effect. These additional estimates are derived from the reported summary data and were not necessarily part of the original statistical analysis.

Results

Baseline demographic characteristics

Table 1: Baseline demographic characteristics of the study population

Variable	Group BUF (n=30)	Group BUN (n=30)	Statistical significance
Age (years), mean±SD	35.90±11.61	38.97±10.70	p=0.29
Weight	Comparable	Comparable	NS
Height	Comparable	Comparable	NS
Male/Female distribution	Comparable	Comparable	NS
ASA I/II distribution	Comparable	Comparable	NS

NS: Not statistically significant.

A total of 60 patients were included, with 30 patients in each treatment group. The demographic characteristics were comparable between groups. The mean age was 35.90±11.61 years in Group BUF and 38.97±10.70 years in Group BUN. The difference was not statistically significant (p=0.29), indicating adequate comparability with respect to age. Mean weight, height, sex distribution and ASA physical status were also reported to be comparable between the two groups, with no statistically

significant baseline differences. The similarity of baseline characteristics is important because differences in age, body habitus, sex distribution or preoperative health status could potentially influence the duration and perception of postoperative pain. The absence of significant baseline differences supports the comparability of the two treatment groups.

Table 2: Comparison of time to first postoperative rescue analgesia

Parameter	Group BUF	Group BUN	Mean difference	p value
Time to first rescue analgesia (min)	379.50±54.11	686.50±129.37	307.00 min	<0.001
Time to first rescue analgesia (hours)	6.33±0.90	11.44±2.16	5.12 h	<0.001

A marked difference was observed in the duration of postoperative analgesia between the two groups. The mean time to first rescue analgesia was 379.50±54.11 minutes in Group BUF compared with 686.50±129.37 minutes in Group BUN. Thus, patients receiving intrathecal nalbuphine remained free from pain requiring rescue analgesia for approximately 11.4 hours compared with approximately 6.3 hours in patients receiving fentanyl.

Table 3: Derived statistical assessment of the primary outcome

Statistical parameter	Estimated value
Mean difference, BUN – BUF	307.0 min
Standard error of difference	25.60 min
Approximate 95% CI	255.2–358.8 min
Standardized mean difference (Cohen's d)	≈3.10
Statistical significance	p<0.001
Relative prolongation with BUN	≈81%

The lower limit of the estimated confidence interval remained more than four hours, indicating that the observed difference was not only statistically significant but also clinically substantial.

Table 4: Comparison of motor block duration

Parameter	Group BUF	Group BUN	Difference
Motor block duration (min), mean±SD	168.83±9.71	170.83±9.48	2.00 min
Approximate duration (hours)	2.81	2.85	0.03 h

The approximately two-minute difference in motor block duration was small and was not considered clinically important. Therefore, the markedly prolonged postoperative analgesia observed with nalbuphine was not accompanied by a comparable prolongation of motor blockade.

Table 5: Overall comparative outcome profile

Outcome	Group BUF: Bupivacaine + Fentanyl	Group BUN: Bupivacaine + Nalbuphine	Interpretation
Dose of hyperbaric bupivacaine	15 mg	15 mg	Identical
Opioid adjuvant	Fentanyl 25 µg	Nalbuphine 1 mg	Different
Sample size	30	30	Equal
Mean age (years)	35.90	38.97	Comparable
Time to first rescue analgesia (min)	379.50	686.50	Markedly longer with nalbuphine
Absolute difference	—	+307 min	Favours nalbuphine
Approximate analgesic duration	6.3 h	11.4 h	Favours nalbuphine
Motor block duration (min)	168.83	170.83	Comparable

The principal observation of this study was the substantially prolonged duration of postoperative analgesia produced by intrathecal nalbuphine. The mean duration of analgesia was approximately 6.3 hours in the fentanyl group.

The corresponding duration was approximately 11.4 hours in the nalbuphine group. Nalbuphine increased the mean time to first rescue analgesia by approximately 307 minutes, equivalent to about 5.1 hours.

Discussion

The present study demonstrated a marked prolongation of postoperative analgesia when nalbuphine 1 mg was used as an intrathecal adjuvant to hyperbaric bupivacaine compared with fentanyl 25 µg. The mean time to first rescue analgesia increased from 379.50 minutes in the fentanyl group to 686.50 minutes in the nalbuphine group. This represents an absolute increase of 307 minutes, or approximately 5.1 hours.

The magnitude of this difference is clinically relevant. The average patient receiving fentanyl required rescue analgesia at approximately 6.3 hours, whereas patients receiving nalbuphine remained free from pain requiring rescue treatment for approximately 11.4 hours. Thus, the analgesic benefit of nalbuphine extended well into the later postoperative period.

These findings are consistent with several clinical studies evaluating nalbuphine as an intrathecal adjuvant. Naaz et al. conducted a randomized double-blind study in 90 patients undergoing lower limb orthopaedic surgery and compared fentanyl with two doses of nalbuphine. Their study supported the analgesic efficacy of intrathecal nalbuphine and demonstrated that nalbuphine could provide prolonged postoperative analgesia when combined with hyperbaric bupivacaine. [1]

Gupta et al. similarly evaluated nalbuphine versus fentanyl as adjuvants to 0.5% hyperbaric bupivacaine in lower limb orthopaedic surgery. Their findings demonstrated prolonged postoperative analgesia with nalbuphine. The findings of the present study are therefore broadly concordant with the existing lower limb orthopaedic literature.[2]

A subsequent randomized controlled trial involving 66 patients undergoing lower limb orthopaedic surgery compared 1 mg nalbuphine with 25 µg fentanyl and a saline control. The study found that the duration of spinal analgesia was 323.18±57.39 minutes with nalbuphine and 287.05±78.87 minutes with fentanyl, although the difference between the opioid groups was not statistically significant. Interestingly, the study also reported a longer motor block duration with fentanyl than with nalbuphine. [3]

The difference between those findings and the much larger treatment effect observed in the present study highlights an important issue: the duration of intrathecal analgesia can vary considerably depending on the study population, surgical procedure, definition of rescue analgesia, bupivacaine dose, opioid dose and postoperative assessment protocol.

Another prospective randomized study of 100 patients receiving 15 mg bupivacaine compared 25 µg fentanyl with 1 mg nalbuphine. In that study, effective analgesia lasted 388±24.88 minutes in the nalbuphine group compared with 304.70±15.76 minutes in the fentanyl group, with a statistically significant difference. [4,5,6] The direction of effect is therefore similar to the present study, although the absolute duration was shorter.

The present study is particularly notable because the difference between groups was approximately 307 minutes, which is considerably larger than the differences reported in some previous studies. This should not necessarily be interpreted as evidence that nalbuphine universally produces a five-hour advantage over fentanyl. Rather, it indicates that, under the conditions of the present study, the interval to first rescue analgesia was substantially prolonged.

An important secondary observation was the similarity of motor block duration. Motor blockade lasted 168.83±9.71 minutes in the fentanyl group and 170.83±9.48 minutes in the nalbuphine group. This finding is important because prolonged postoperative analgesia can sometimes be associated with prolonged neuraxial blockade. In the present study, however, the approximately five-hour extension in analgesia occurred despite virtually identical motor block duration. This supports the interpretation that the additional analgesic effect was related to the pharmacological action of nalbuphine rather than simply persistence of the local anaesthetic block. [7,8]

Nalbuphine has a distinctive opioid receptor profile. It is predominantly a κ-opioid receptor agonist with µ-opioid receptor antagonist activity. Activation of spinal κ receptors can suppress nociceptive transmission, while its µ-antagonist properties may limit some of the adverse effects associated with pure µ-opioid agonists.

The overall literature supports the ability of nalbuphine to prolong spinal analgesia, although the magnitude of benefit varies among studies. A systematic review and meta-analysis evaluating nalbuphine as an adjuvant to spinal anaesthesia concluded that nalbuphine can influence sensory and motor block characteristics and prolong postoperative analgesia, while also emphasizing variability among individual studies. [8,9]

More recent evidence also supports nalbuphine as an alternative intrathecal opioid adjuvant. A 2026 systematic review and meta-analysis involving caesarean-section studies found a modest prolongation of effective analgesia with nalbuphine compared with fentanyl, although substantial heterogeneity and very low certainty of evidence limited the strength of the conclusion. [10,11,12] The prolonged interval before rescue analgesia may offer several potential clinical advantages. First, it can reduce the need for early systemic analgesic administration. Second, it may provide improved comfort during the transition from recovery-room care to the ward. Third, sustained analgesia may facilitate early physiotherapy and mobilisation by preventing a sudden increase in pain as spinal anaesthesia regresses.

Safety Considerations: Intrathecal opioid administration requires appropriate patient monitoring because opioid-related adverse effects may include nausea, vomiting, pruritus, urinary

retention, sedation and respiratory depression. The theoretical advantage of nalbuphine arises from its mixed agonist-antagonist profile.

The present study's conclusion should nevertheless be restricted to the outcomes actually evaluated. Since the supplied parent-study results do not provide detailed numerical frequencies of every adverse event, it would be inappropriate to claim definitively that nalbuphine was safer than fentanyl in this particular cohort.

Strengths of the Study: The present study has several strengths. First, it used a randomized prospective design, reducing the potential for systematic differences between treatment groups. Second, the two groups received an identical dose of hyperbaric bupivacaine, allowing the opioid adjuvant to remain the principal treatment difference. Third, the study used a clinically meaningful endpoint—time to first rescue analgesia—which directly reflects the duration of analgesic benefit perceived by the patient. Fourth, the study demonstrated that prolonged analgesia was achieved without a clinically meaningful prolongation of motor blockade.

Limitations: The study has several limitations that should be considered when interpreting its findings. First, the sample size was relatively small, with only 30 patients in each group. Although the difference in the primary endpoint was highly statistically significant, a larger multicentre trial would provide greater precision and generalisability. Second, only ASA I and II patients aged 20–55 years were included. Therefore, the findings may not be directly applicable to elderly patients, patients with significant systemic disease or high-risk surgical populations. Third, the study included lower limb surgery but did not provide sufficiently detailed stratification by specific surgical procedure. The intensity and duration of postoperative pain can vary considerably between procedures. Fourth, the primary outcome was time to first rescue analgesia. Serial pain scores, cumulative analgesic consumption at 6, 12 and 24 hours, patient satisfaction and functional recovery would provide a more comprehensive assessment of postoperative analgesia. Fifth, rescue analgesia consisted of either paracetamol 1 g or diclofenac 75 mg. If the choice of rescue medication was not standardized, differences in the potency or duration of these agents could potentially influence subsequent postoperative analgesic outcomes. Finally, although nalbuphine demonstrated a substantial analgesic advantage, the present data do not establish superiority with respect to all safety outcomes. Detailed adverse-event data would be necessary before making a definitive claim that nalbuphine is safer than fentanyl.

Conclusion

The present randomized prospective study demonstrated a marked prolongation of postoperative analgesia following intrathecal administration of nalbuphine 1 mg with 15 mg hyperbaric bupivacaine compared with fentanyl 25 µg with the same dose of bupivacaine in patients undergoing lower limb surgery.

The mean time to first rescue analgesia was 686.50±129.37 minutes with nalbuphine compared with 379.50±54.11 minutes with fentanyl, representing an absolute difference of approximately 307 minutes or 5.1 hours. This difference was highly statistically significant ($p<0.001$).

Importantly, motor blockade duration was comparable between the groups, suggesting that the prolonged postoperative analgesia associated with nalbuphine was not simply attributable to prolonged motor blockade.

Overall, intrathecal nalbuphine 1 mg appears to be an effective adjuvant to hyperbaric bupivacaine for extending postoperative analgesia following lower limb surgery. Nevertheless, larger multicentre randomized trials incorporating serial pain scores, cumulative rescue analgesic consumption, patient satisfaction, functional recovery and standardized adverse-event assessment are warranted to establish its comparative clinical and safety advantages more definitively.

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