

HAEMODYNAMIC STABILITY AND ADVERSE EFFECTS OF INTRATHECAL NALBUPHINE VERSUS FENTANYL AS ADJUVANTS TO HYPERBARIC BUPIVACAINE IN LOWER LIMB SURGERY

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Abstract

Background: Intrathecal opioids improve the quality and duration of spinal anaesthesia but may produce haemodynamic and opioid-related adverse effects. Nalbuphine has been proposed as an alternative to fentanyl because of its potentially favourable adverse-effect profile. This study compared perioperative haemodynamic changes and adverse effects following intrathecal nalbuphine or fentanyl combined with hyperbaric bupivacaine.

Methods: Sixty patients aged 20–55 years with ASA physical status I or II undergoing elective lower limb surgery under spinal anaesthesia were randomized into two groups of 30. Group BUF received hyperbaric bupivacaine 15 mg with fentanyl 25 µg, while Group BUN received hyperbaric bupivacaine 15 mg with nalbuphine 1 mg. Heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure were monitored at predefined perioperative intervals. Adverse effects including hypotension, bradycardia, postoperative nausea and vomiting, shivering, respiratory depression and pruritus were recorded.

Results: There were no statistically significant between-group differences in mean heart rate, systolic blood pressure, diastolic blood pressure or mean arterial pressure at the recorded intervals. Both groups demonstrated the expected peri-spinal reduction in cardiovascular parameters during the early intraoperative period, followed by recovery. Adverse events were infrequent and comparable. Postoperative nausea and vomiting occurred in 3 patients (10%) in BUN and 2 patients (6.7%) in BUF. Hypotension occurred in 2 patients (6.7%) in each group, bradycardia in 1 patient (3.3%) in each group and shivering in 1 patient (3.3%) in each group. No significant difference in complication rates was observed (p=0.99).

Conclusion: Intrathecal nalbuphine 1 mg and fentanyl 25 µg, when added to hyperbaric bupivacaine, demonstrated comparable haemodynamic stability and a low incidence of adverse effects. Nalbuphine was not associated with increased cardiovascular instability or clinically important opioid-related complications.

Keywords: nalbuphine; fentanyl; hyperbaric bupivacaine; spinal anaesthesia; haemodynamics; hypotension; bradycardia; adverse effects.

INTRODUCTION

Spinal anaesthesia remains one of the most frequently employed regional anaesthetic techniques for lower abdominal, pelvic and lower limb surgical procedures. Its major advantages include rapid onset, dense sensory and motor blockade, avoidance of airway instrumentation, reduction in systemic anaesthetic requirements and provision of satisfactory surgical conditions. Nevertheless, spinal anaesthesia is associated with characteristic physiological alterations resulting primarily from blockade of sympathetic nerve fibres.[1]

Sympathetic blockade produces peripheral arterial and venous vasodilatation, decreases systemic vascular resistance and reduces venous return to the heart. Depending on the extent and level of the block, these effects may result in varying degrees of hypotension. Blockade involving the cardioaccelerator fibres and reduction in venous return may additionally contribute to bradycardia. Although these changes are usually transient and readily manageable in healthy patients, pronounced cardiovascular instability can become clinically relevant, particularly in susceptible individuals.[2]

Hyperbaric bupivacaine is widely used for subarachnoid block because it produces reliable sensory and motor blockade of adequate duration for many lower limb procedures. However, prolonging postoperative analgesia by increasing the dose of local anaesthetic may also increase the intensity and duration of sympathetic and motor blockade. Consequently, adjuvants are frequently combined with intrathecal local anaesthetics to enhance analgesia without substantially increasing the local anaesthetic dose.[3]

Opioids are among the most extensively investigated intrathecal adjuvants. They act predominantly through opioid receptors within the dorsal horn of the spinal cord and can enhance nociceptive modulation without necessarily producing additional sympathetic or motor blockade. Fentanyl is a highly lipophilic synthetic µ-opioid receptor agonist. Its rapid spinal cord penetration and relatively limited rostral spread make it a commonly selected intrathecal opioid. However, adverse effects such as pruritus, nausea, vomiting and respiratory depression remain potential concerns with neuraxial opioids.[4,5]

Nalbuphine is a semisynthetic opioid with mixed agonist–antagonist characteristics, predominantly exhibiting κ-opioid receptor agonist and µ-opioid receptor antagonist properties. The κ-receptor-mediated spinal analgesic effect provides a pharmacological basis for its intrathecal administration. Its mixed opioid receptor activity has generated interest

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regarding whether it can provide effective neuraxial analgesia while limiting some of the adverse effects associated with conventional μ -opioid receptor agonists.

For an intrathecal adjuvant to be clinically useful, enhancement of anaesthesia or analgesia should not occur at the expense of cardiovascular or respiratory safety. Comparison of haemodynamic responses and adverse-effect profiles is therefore important when selecting between intrathecal opioid adjuvants.

The present study was undertaken to compare perioperative haemodynamic parameters and adverse effects associated with intrathecal nalbuphine and fentanyl when administered with hyperbaric bupivacaine in patients undergoing elective lower limb surgery.

MATERIALS AND METHODS

This randomized prospective study was conducted in the Department of Anaesthesiology, Thumbay Hospital New Life, Hyderabad, over six months. Sixty patients aged 20–55 years belonging to ASA I or II and undergoing lower limb surgery were enrolled. Patients with higher ASA grades, significant cardiovascular, neurological, hepatic, renal or metabolic disease, coagulation abnormalities, drug hypersensitivity, contraindications to spinal anaesthesia or local sepsis were excluded.

Participants were randomized using sealed envelopes into two groups. BUF received 15 mg hyperbaric bupivacaine plus fentanyl 25 μ g intrathecally, while BUN received 15 mg hyperbaric bupivacaine plus nalbuphine 1 mg intrathecally.

Heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, respiratory rate, oxygen saturation and ECG were monitored. Measurements were obtained every two minutes for the first five minutes, every five minutes until 30 minutes, every 15 minutes until 60 minutes and subsequently every 30 minutes until 150 minutes or completion of surgery. Postoperative parameters were recorded hourly.

Hypotension was defined in the thesis as a fall in systolic blood pressure of more than 30% from baseline or systolic pressure below 90 mmHg. Bradycardia was defined as heart rate below 60 beats/minute. Respiratory depression was defined as respiratory rate below 8/minute or SpO₂ below 85%.

RESULTS

Table 1- Demographic and baseline characteristics of the study participants

Parameter	Group BUN (N=30)	Group BUF (N=30)	Statistical significance
Age (years)	Comparable	Comparable	NS
Weight (kg)	Comparable	Comparable	NS

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Parameter	Group BUN (N=30)	Group BUF (N=30)	Statistical significance
Height (cm)	Comparable	Comparable	NS
Sex distribution	Comparable	Comparable	NS
ASA physical status	ASA I-II	ASA I-II	NS

The two groups were comparable with respect to age, weight, height, sex and ASA physical status.

Table 2- Comparison of heart rate at different perioperative intervals

Time interval	BUN (beats/min)	BUF (beats/min)
Baseline	75.50 ± 4.66	76.30 ± 8.19
5 min	72.03 ± 5.46	75.40 ± 11.18
15 min	69.40 ± 5.73	73.33 ± 9.63
30 min	68.13 ± 6.60	70.63 ± 9.32
60 min	67.43 ± 5.85	69.37 ± 9.17
120 min	69.70 ± 5.68	71.33 ± 9.50

Baseline mean heart rate was 75.50±4.66 beats/min in BUN and 76.30±8.19 beats/min in BUF. Mean heart rate decreased progressively during the early intraoperative period, reaching 68.13±6.60 beats/min in BUN and 70.63±9.32 beats/min in BUF at 30 minutes. There were no statistically significant between-group differences at the reported intervals.

Table 3. Selected perioperative haemodynamic parameters

Time	HR BUN	HR BUF	SBP BUN	SBP BUF	MAP BUN	MAP BUF
Baseline	75.50±4.66	76.30±8.19	121.63±8.89	123.00±10.87	91.27±6.26	92.13±8.00
5 min	72.03±5.46	75.40±11.18	110.60±9.67	113.93±14.24	82.60±7.45	84.53±10.27
15 min	69.40±5.73	73.33±9.63	105.60±12.20	109.90±15.19	78.33±8.91	81.17±10.77
30 min	68.13±6.60	70.63±9.32	104.10±13.42	107.03±15.91	76.97±9.79	79.57±12.05
60 min	67.43±5.85	69.37±9.17	107.07±11.27	107.50±13.94	79.63±8.77	80.73±10.31
120 min	69.70±5.68	71.33±9.50	108.04±8.15	108.75±10.77	80.44±6.55	81.42±8.86

There was no statistically significant difference between groups in mean systolic blood pressure at any recorded interval. Similarly, diastolic blood pressure did not differ significantly between the groups. Mean arterial pressure was also comparable throughout the monitored period. For example, baseline MAP was 91.27±6.26 mmHg in BUN and 92.13±8.00 mmHg in BUF, while at 30 minutes it was 76.97±9.79 and 79.57±12.05 mmHg, respectively.

Table 4. Comparison of complications

Adverse effect	BUN n (%)	BUF n (%)	p value
Postoperative nausea and vomiting	3 (10.0)	2 (6.7)	0.99
Bradycardia	1 (3.3)	1 (3.3)	0.99
Hypotension	2 (6.7)	2 (6.7)	0.99
Shivering	1 (3.3)	1 (3.3)	0.99

No statistically significant difference was observed in any of the recorded complications. No patient developed respiratory depression, pruritus, desaturation, euphoria or dysphoria in either group.

DISCUSSION

The present study evaluated the haemodynamic stability and adverse-effect profiles of nalbuphine and fentanyl when administered intrathecally as adjuvants to hyperbaric bupivacaine for lower limb surgery. The principal finding was that both combinations produced similar cardiovascular responses following spinal anaesthesia. Although reductions in HR, SBP and MAP were observed during the early intraoperative period, these changes occurred in both groups and no significant between-group differences were demonstrated.

A reduction in arterial blood pressure following spinal anaesthesia is an expected physiological response. Subarachnoid administration of a local anaesthetic blocks sympathetic efferent fibres, resulting in arterial and venous vasodilatation. Venodilatation causes pooling of blood in the lower extremities and splanchnic circulation, thereby decreasing venous return and cardiac preload. Simultaneous reduction in systemic vascular resistance contributes to the fall in arterial pressure.

The temporal pattern in the present study supports this mechanism. SBP decreased from 121.63±8.89 mmHg at baseline to 104.10±13.42 mmHg at 30 minutes in BUN, whereas in BUF it decreased from 123.00±10.87 to 107.03±15.91 mmHg. MAP demonstrated a corresponding reduction. The similarity between the groups is clinically important because it indicates that addition of nalbuphine did not produce greater cardiovascular depression than fentanyl.

Heart rate also decreased following spinal anaesthesia in both groups. In BUN, HR decreased from 75.50±4.66 beats/min at baseline to 68.13±6.60 beats/min at 30 minutes, while the corresponding reduction in BUF was from 76.30±8.19 to 70.63±9.32 beats/min. Several mechanisms may contribute to bradycardia during spinal anaesthesia, including blockade of sympathetic cardioaccelerator fibres, decreased venous return and alteration of autonomic balance. Despite the decline in mean HR, clinically defined bradycardia occurred in only one

patient in each group. The identical incidence of clinically significant bradycardia suggests that nalbuphine did not confer additional chronotropic instability compared with fentanyl.

The present findings are broadly consistent with the studies referenced in the parent work. Gupta *et al.* compared intrathecal nalbuphine and fentanyl as adjuvants to hyperbaric bupivacaine for lower limb orthopaedic procedures and reported comparable haemodynamic characteristics between treatment groups. Their findings support the observation that nalbuphine can be administered intrathecally without producing substantial additional cardiovascular instability. Bisht and Rashmi similarly compared intrathecal fentanyl and nalbuphine in a prospective randomized study. Their observations contributed to the evidence supporting nalbuphine as a clinically useful neuraxial adjuvant. Naaz *et al.* evaluated the analgesic effects of intrathecal nalbuphine and fentanyl in lower limb orthopaedic surgery. The study also supports the feasibility of nalbuphine as an alternative intrathecal opioid adjuvant. [1-5]

Earlier work by Culebras *et al.* [2] investigating intrathecal nalbuphine in comparison with morphine demonstrated the clinical potential of nalbuphine for neuraxial analgesia. Lin also investigated subarachnoid nalbuphine in combination with local anaesthesia, providing earlier evidence regarding its spinal analgesic effects.

Collectively, these findings support the haemodynamic observations of the present study, in which nalbuphine and fentanyl produced comparable cardiovascular profiles.

Hypotension is one of the most clinically relevant complications associated with spinal anaesthesia. In the present study, only 2 patients (6.7%) in each group fulfilled the predefined criteria for hypotension. This finding is particularly relevant because a theoretical concern with the addition of an opioid adjuvant could be potentiation of anaesthesia-associated cardiovascular depression. The identical incidence of hypotension indicates that nalbuphine did not increase this risk relative to fentanyl. [6]

The haemodynamic changes observed should also be distinguished from clinically defined hypotension. Mean blood pressure values decreased after establishment of spinal blockade, but most patients remained within clinically acceptable limits and therefore did not meet the predefined hypotension criteria.

PONV occurred in 10% of patients receiving nalbuphine compared with 6.7% receiving fentanyl. Although this represented a small numerical difference, it was not statistically significant.

Nausea and vomiting following spinal anaesthesia may have multifactorial origins. In addition to the direct effects of neuraxial opioids, hypotension, vagal predominance, surgical factors and individual susceptibility may contribute. Consequently, the small difference observed in the present study cannot be attributed solely to the choice of intrathecal opioid.

No patient in either group experienced pruritus. Pruritus is a well-recognized complication of neuraxial μ -opioid receptor agonists and may adversely affect patient comfort even when it is not medically serious. The absence of pruritus in the current sample represents a favourable finding for both regimens. However, because of the modest sample size, definitive conclusions regarding differences in the incidence of uncommon opioid-related adverse effects cannot be drawn. Shivering was observed in one patient (3.3%) in each group. The identical incidence suggests that the choice between nalbuphine and fentanyl had no appreciable influence on shivering in this study. [7,8]

Perioperative shivering is multifactorial and may be related to redistribution of body heat, impairment of thermoregulatory responses by neuraxial anaesthesia, operating-room temperature, intravenous fluid administration and patient-specific factors. [9]

Clinical Implications

The findings have several potential clinical implications. First, nalbuphine 1 mg can be combined with 15 mg hyperbaric bupivacaine without evidence of greater cardiovascular instability than that observed with fentanyl 25 μ g in relatively healthy adults undergoing lower limb surgery.

Second, the incidences of clinically significant hypotension and bradycardia were identical between groups, suggesting that the cardiovascular effects were predominantly attributable to spinal sympathetic blockade rather than to a meaningful difference between the two opioid adjuvants.

Third, no respiratory depression or pruritus was observed with nalbuphine in the study population. Together with its favourable haemodynamic profile, this observation supports further consideration of nalbuphine as an alternative intrathecal adjuvant.

Finally, selection of an intrathecal adjuvant should not be based solely on the duration of analgesia. Haemodynamic stability, respiratory safety, postoperative nausea and vomiting, pruritus and overall patient tolerability should also influence clinical decision-making. The present findings indicate that nalbuphine performed favourably across these safety outcomes.

Strengths of the Study

The prospective randomized design represents an important methodological strength because random allocation helps minimize selection bias and improves comparability between groups. Both groups received the same dose of hyperbaric bupivacaine, allowing the principal difference in spinal drug combination to be the opioid adjuvant. Furthermore, haemodynamic parameters were monitored repeatedly during the perioperative period rather than relying only on baseline and isolated postoperative observations. This enabled evaluation of the temporal pattern of cardiovascular response after establishment of spinal anaesthesia.

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The study also used predefined clinical criteria for hypotension, bradycardia and respiratory depression, providing clinically interpretable safety outcomes.

Limitations

Several limitations should be considered when interpreting the findings. First, the sample size was relatively small, with only 30 patients in each group. The study therefore had limited ability to detect small differences or rare adverse events such as severe respiratory depression. Second, only patients aged 20–55 years with ASA physical status I or II were included. The findings therefore cannot automatically be generalized to elderly patients, patients with significant cardiovascular disease, ASA III–IV patients or those undergoing emergency surgery. Third, a bupivacaine-only control group was not included. Consequently, the independent contributions of nalbuphine and fentanyl to the observed haemodynamic changes cannot be separated from the effects of the spinal local anaesthetic itself.

CONCLUSION

Intrathecal nalbuphine 1 mg and fentanyl 25 µg, when administered as adjuvants to 15 mg hyperbaric bupivacaine for spinal anaesthesia in lower limb surgery, demonstrated comparable perioperative haemodynamic profiles.

Both groups showed an expected early decline in heart rate, systolic blood pressure and mean arterial pressure following spinal anaesthesia, followed by stabilization. These changes did not differ significantly between the nalbuphine and fentanyl groups.

Clinically significant hypotension occurred in 6.7% of patients in each group, while bradycardia and shivering each occurred in 3.3%. PONV occurred in 10% of patients receiving nalbuphine and 6.7% receiving fentanyl, without a statistically significant difference. No respiratory depression, clinically important desaturation or pruritus was observed.

Within the limitations of this study, intrathecal nalbuphine demonstrated a safety and haemodynamic profile comparable to fentanyl. Nalbuphine may therefore be considered a useful alternative intrathecal opioid adjuvant to hyperbaric bupivacaine for lower limb surgery in appropriately selected patients.

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