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ORIGINAL RESEARCH

Effect of Ropivacaine Combined with Nalbuphine in Erector Spinae Plane Block on Postoperative Analgesia in Lumbar Trauma Surgery: A Single-Center Randomized Controlled Trial

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Background: The erector spinae plane block (ESPB) has been increasingly utilized for postoperative analgesia in thoracic, abdominal, and spinal surgeries. This study evaluated the postoperative analgesic outcomes of ESPB with nalbuphine as a ropivacaine adjuvant for lumbar trauma surgery.

Methods: This randomized double-blind clinical trial included 57 participants who underwent lumbar trauma surgery. Ultrasound-guided ESPB was performed with 0.375% ropivacaine (Group R) and 0.375% ropivacaine combined with 10 mg nalbuphine (Group N); 20 mL was used per side. The primary outcome measure was the time to first postoperative remedial analgesia. The secondary outcome measures included the Numerical Rating Scale (NRS) scores at rest and during movement, cumulative sufentanil consumption after surgery, intraoperative dosage of remifentanil and sufentanil, time to first off-bed, time to first flatus, and length of hospital stay.

Results: The mean difference in the time to first postoperative remedial analgesia (Group N vs Group R, 489±52 min vs 391±23 min) was 98 min (95% CI, 76 to 119). Kaplan–Meier survival analysis revealed an increasing pain-free population in Group N and an increasing pain-free duration. The log-rank (Mantel–Cox) test showed that the hazard ratio (HR, Group N/Group R) was 0.225 (95% CI, 0.114 to 0.443). Group N showed decreased sufentanil consumption compared with Group R at 4–8 h, 8–12 h and 0–24 h after surgery ($P<0.001$).

Conclusion: ESPB with nalbuphine in combination with ropivacaine significantly prolonged the duration of analgesia and reduced postoperative analgesic demands compared to ropivacaine alone.

Keywords: analgesia, nerve block, nalbuphine, ropivacaine, ultrasound interventional

Introduction

The posterior screw and rod fixation technique is the primary surgical treatment for lumbar trauma; however, severe postoperative pain frequently impedes rapid recovery. Although opioids provide analgesia for moderate to severe pain, side effects, including nausea, vomiting, and respiratory depression, may arise. Recently, regional nerve block techniques have assumed a greater role in multimodal analgesic regimens because they provide substantial postoperative pain relief and facilitate opioid reduction. First described in 2016 by Forero et al,[1] the erector spinae plane block (ESPB) has been increasingly used in thoracic, abdominal, and spinal surgery analgesia. ESPB can deeply inject local anesthetics into the fascial plane between the transverse process of the vertebral body and the erector spinae muscle.[2] Leveraging the interconnected nature of the erector spinae muscle's fascial planes across the thoracic and lumbar segments, local anesthetics are able to disperse both cranially and caudally. This distribution effectively blocks the posterior branches of the spinal nerve within a defined range, with a blocking range of T_8~S_2.[3] To address this, the addition of adjuvants to

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local anesthetics has become a focal point in clinical research, with the goal of extending their analgesic properties. Adjuvants such as morphine, fentanyl, sufentanil and other drugs have been used in combination with local anesthetics could enhance the blocking effect and prolong the analgesic time,[4–7] however, with limited success.

As a mixed opioid receptor agonist-antagonist, nalbuphine provides analgesia through κ-receptor activation, while its μ-receptor antagonism attenuates side effects such as respiratory depression, pruritus, nausea, and vomiting. Bindra et al[8] used nalbuphine as an adjuvant to bupivacaine in spinal anesthesia and reported that the analgesia time of bupivacaine was significantly prolonged. Das et al[9] showed similar effects of adding nalbuphine into brachial plexus blocks. However, limited evidence exists regarding nalbuphine as a ropivacaine adjuvant in plane blocks.

Therefore, we conducted a randomized, double-blinded, controlled trial utilizing nalbuphine as a ropivacaine adjuvant for ESPB to evaluate postoperative analgesic outcomes following lumbar trauma surgery.

Materials and Methods

Study Design and Patients Enrollment

This single-center, prospective, randomized, double-blinded, controlled trial was conducted from July 2022 to September 2023 after ethics approval (Ref: 2022–11) from the Second People's Hospital of Wuhu. The study was registered at the Chinese Clinical Trial Registry (ChiCTR2200061127).

Patients aged 18–65 years with American Society of Anesthesiologists classification I–II who underwent elective lumbar surgery were included. The exclusion criteria were severe spinal deformity, local anesthetic allergy, severe cardiopulmonary disease, obesity (BMI > 30 kg/m^2), coagulopathy, infection, hepatic/renal dysfunction, preoperative sedative/analgesic use, psychosis, cognitive dysfunction resulting in an inability to cooperate, a procedure duration of <60 or >300 minutes, ICU admission, or refusal of follow-up. All patients were trained on the Numerical Rating Scale (NRS) and patient-controlled analgesia (PCA) preoperatively.

Ethical Statement

Research involving human subjects adhered to the principles outlined in the Declaration of Helsinki and obtained approval from the Ethics Committee of the second People's Hospital of Wuhu. All participants provided written informed consent prior to enrollment.

Patient Grouping, Randomization and Blinding Methods

According to computer-generated random numbers, the patients were randomly allocated at a 1:1 ratio to the ropivacaine group (Group R) or the nalbuphine-ropivacaine group (Group N). The anesthesiologist received random numbers from the investigators and divided the patients into two groups. The study drugs were packaged in containers with the same color and 20 mL capacity. The anesthesiologist who was responsible for implementing ESPB in this study was not involved in the subsequent analyses. Personnel involved in anesthesia management, intraoperative data recording, and collection of various postoperative scores and related data were blinded to group assignments. The surgeon, the patients themselves, and their family members were also blinded.

Anesthesia Management

After connecting the patient to standard monitoring equipment (ULTRAVIEW SL® 2700, Spacelabs Health care, Inc)., radial artery catheterization was performed successfully under local anesthesia. General anesthesia was then induced with intravenous sufentanil 0.4 to 0.6 μg/kg, propofol 1 to 2 mg/kg, and rocuronium 0.8 mg/kg, followed by intubation. Anesthesia was maintained with propofol (2 to 4 mg/kg/h), remifentanil (0.1 to 0.2 μg/kg/min), sevoflurane and intermittent rocuronium, targeting a bispectral index (BIS) of 40 to 60. Volume control ventilation mode was used with the following settings: tidal volume, 6 to 8 mL/kg; respiratory rate, 12 to 15 breaths/min. The partial pressure of end-expiratory carbon dioxide ($ETCO_2$) was maintained between 35 and 45 mmHg.

During anesthesia, 0.2 μg/kg sufentanil was injected intravenously if the blood pressure or heart rate increased by more than 20%. The intraoperative mean arterial pressure (MAP) was maintained at no less than 55 mmHg and the

systolic blood pressure (SBP) at no less than 90 mmHg, and vasoactive drugs (phenylephrine) were injected intravenously if necessary. Ondansetron (8 mg) was administered to reduce postoperative nausea and vomiting (PONV).

After surgery, the patients were awakened, extubated, and admitted to the postanesthesia care unit (PACU). Patients were released to the orthopedics ward when they met the PACU discharge standard.

Analgesic Protocol and Evaluation of Pain

All patients received 50 mg of flurbiprofen axetil intravenously before skin suturing. Analgesia was initiated with 100 μg of sufentanil and 8 mg of ondansetron in 100 mL of saline, with a 5 μg loading dose, 2 mL/h background infusion, and 0.5 mL demand dose with a 15 min lockout. When the NRS score was ≥4, 0.05 mg/kg intravenous oxycodone was administered as needed. The NRS pain score ranged from 0–10, with 0 indicating no pain, 1–3 indicating mild pain, 4–6 indicating moderate pain, and 7–10 indicating severe pain.

Erector Spinae Plane Block Procedure

After intubation, ESPB was performed in the surgical position (prone position) under ultrasonic guidance with a microconvex transducer (Mindray TE7: C_5-2s). After skin preparation with iodophor disinfectant, the ultrasound probe wrapped with a sterile protective sleeve was placed at the midsagittal position of the vertebral body and moved toward the paravertebral region to obtain the best visual field display. After ultrasonography revealed the L_2 lumbar transverse process and the erector spinal muscle, a small amount (2–4 mL) of physiological saline was injected into the puncture needle using the in-plane needle insertion technique to confirm the position of the needle tip. The same method was used for the opposite side. Patients received 20 mL of 0.375% (75 mg) ropivacaine (Group R) or 0.375% (75 mg) ropivacaine plus 10 mg nalbuphine (Group N) bilaterally.

Outcome Measures

The primary outcome measure was the time to first postoperative remedial analgesia (from the end of surgery to the first administration of oxycodone). The secondary outcome measures of the study were NRS scores at rest and during movement at 4 h, 6 h, 8 h, 10 h, 12 h, 24 h and 48 h after extubation; cumulative sufentanil consumption at 0–4 h, 4–8 h, 8–12 h, 12–24 h and 0–24 h after surgery (oxycodone 1 mg = sufentanil 1 μg); intraoperative dosage of remifentanil and sufentanil; time to first off-bed; time to first flatus; and length of hospital stay. The incidences of PONV, dizziness, skin itching, local anesthetic intoxication and hypoxemia ($SpO_2 \leq 93\%$) and patient satisfaction with pain management (three levels: not satisfied, general satisfied, and very satisfied) were also recorded.

Sample Size Calculation

PASS 15.0 software was used to calculate the sample size. The estimated sample size was calculated from the primary outcome of the time to first postoperative remedial analgesia. In the preliminary experiment, with 10 patients in each group, the times to first postoperative remedial analgesia in Groups R and N were 389.7 minutes and 452.7 minutes, respectively, with an average standard deviation of 70. Given a power of 90% and $\alpha = 0.05$, the sample size was determined to be 54, with 27 subjects in each arm using a 1:1 ratio. Considering a possible 10% loss to follow-up, 60 patients were included in this trial (30 patients per group).

Statistical Analysis

Statistical analysis was conducted using SPSS 26.0 and GraphPad Prism 8.0 software. Continuous data were analyzed and tested for distribution using *Shapiro–Wilk's* test. Normally distributed data are presented as the mean ± SD and were analyzed by an independent samples *t* test to compare groupwise differences in the outcome parameters, and the effect values are expressed as the mean difference and its 95% CI. Nonnormally distributed data are expressed as the median [interquartile range] and were analyzed by a *Mann–Whitney U*-test, and the effect values are represented by the median difference and its 95% CI (Hodges–Lehmann method). Categorical variables are reported as numbers (%) and were compared using the χ^2 test or *Fisher's exact* test, as appropriate. The MAP and HR of patients at different time points during surgery were analyzed using repeated-measures *ANOVA*. *Kaplan–Meier* survival analysis and *the Log rank* test

were used to analyze the time to first postoperative remedial analgesia. $P < 0.05$ was considered to indicate statistical significance.

Results

A total of 71 patients were screened, 11 of whom did not meet the inclusion criteria (3 patients were ASA III, 5 patients were over 65 years old, and 3 patients had a BMI > 30 kg/m^2). Finally, 60 patients were divided into two groups. Two patients in Group R were transferred to the intensive care unit after surgery with acute blood loss exceeding 1000 mL. The duration of surgery in one patient in Group N was greater than 300 min. Accordingly, 28 and 29 patients were analyzed in Groups R and N, respectively (Figure 1). The baseline and intraoperative characteristics did not significantly differ between the groups (Table 1).

The time to first postoperative remedial analgesia was longer in Group N than in Group R (489 ± 52 min vs 391 ± 23 min), and the mean difference was 98 min (95% CI, 76 to 119; $P < 0.001$). Kaplan–Meier survival analysis revealed

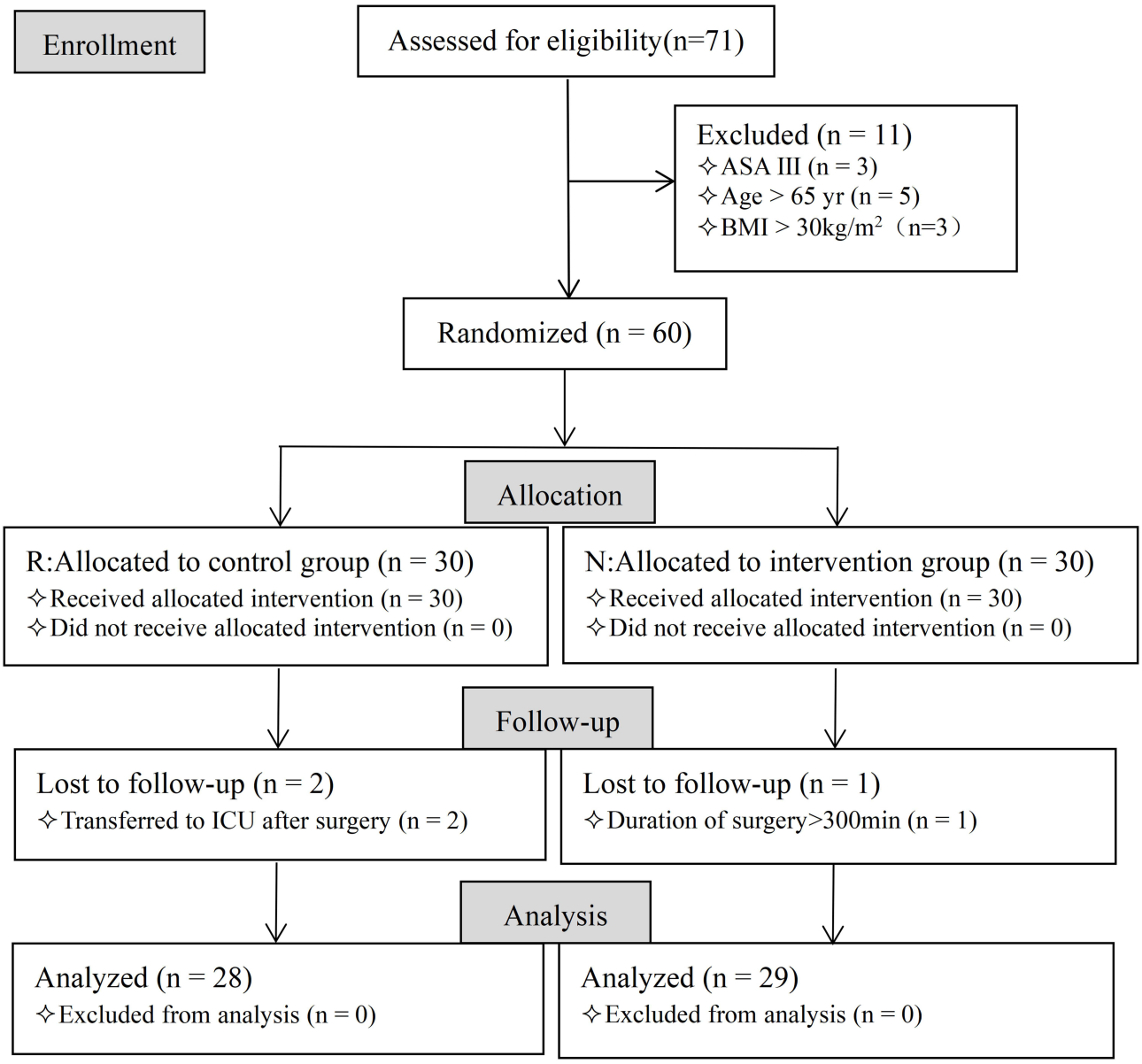

Figure 1 Flow diagram of the present study.

Table 1 Demographic and Operative Characteristics of Study Patients

	R(n=28)	N(n=29)	F/χ^2	P
Age (years)*	52.79±4.43	52.59±6.32	0.138	0.891
BMI (kg/m^2)*	25.14±1.94	25.21±1.86	0.127	0.899
Gender†			0.193	0.661
Male (n, %)	18 (64.3)	17 (58.6)		
Female (n, %)	10 (35.7)	12 (41.4)		
ASA status†			0.144	0.704
I (n, %)	8 (28.6)	7 (24.1)		
II (n, %)	20 (71.4)	22 (75.9)		
Comorbid disease†				
Hypertension (n, %)	9 (32.1)	11 (37.9)	0.210	0.647
Diabetes (n, %)	7 (25.0)	6 (20.7)	0.150	0.698
Intraoperative remifentanil (μg)*	1714.64±135.66	1690.35±170.12	0.595	0.554
Intraoperative sufentanil (μg)*	50.54±6.43	50.17±6.19	0.217	0.829
Anesthesia time (min)*	147.86±12.65	151.03±14.48	0.881	0.382
Surgery procedure duration (min)*	129.82±11.34	133.97±14.17	1.216	0.229
Extubation time (min)*	16.14±2.12	15.03±2.57	1.772	0.082
Blood loss (mL)*	430.71±73.08	450.00±92.58	0.871	0.388

Notes: *Independent sample *t*-test. †The χ2 test. Values are presented as number (%) or mean ±standard deviation.

an increasing pain-free population and pain-free time in Group N, and the log-rank (Mantel Cox) test showed that the hazard ratio (HR, Group N/Group R) was 0.225 (95% CI, 0.114 to 0.443; $P < 0.001$) (Figure 2).

The NRS scores at rest at 8 h, 10 h and 12 h after surgery in Group N were significantly lower than those in Group R ($P < 0.05$). There was no statistically significant difference between the two groups at other time points ($P > 0.05$) (Supplementary Table 1, Figure 3A). NRS scores during movement at 8 h and 10 h after surgery in Group N were significantly lower than those in Group R ($P < 0.05$). There was no statistically significant difference between the groups at other time points ($P > 0.05$) (Supplementary Table 1, Figure 3B).

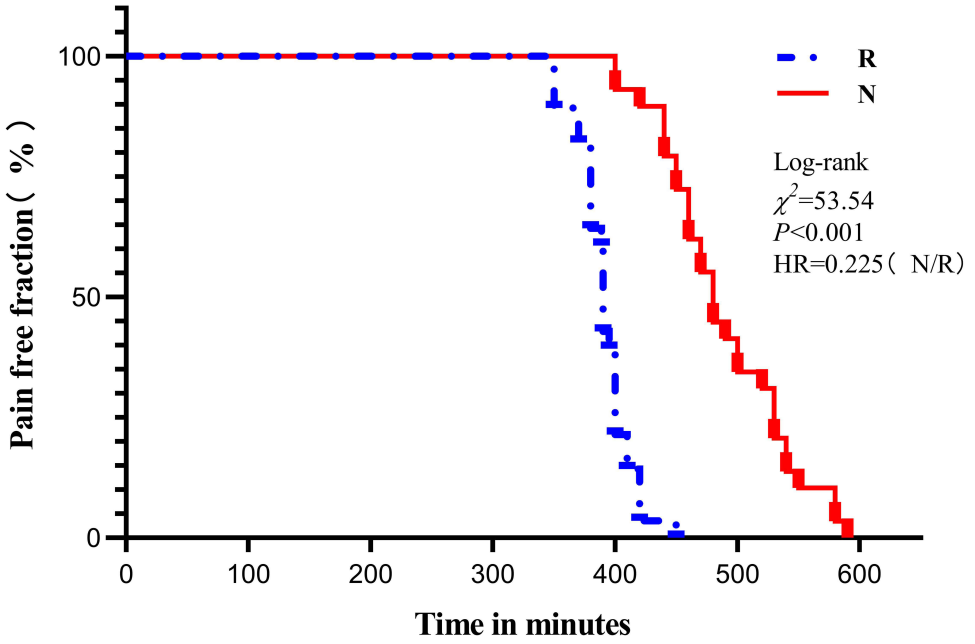

Figure 2 Time to first postoperative remedial analgesia. Kaplan–Meier survival plot showing increased pain-free population in Group N. The Cox hazard ratio showed that there was a 0.225-fold decreased risk of pain in Group N.

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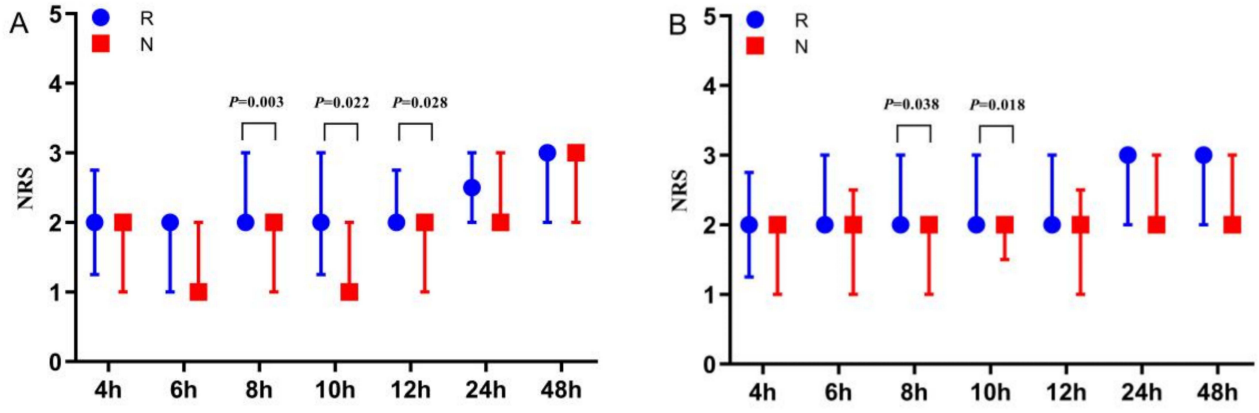

Figure 3 NRS scores at rest and during movement. The NRS scores at rest (**A**) and during movement (**B**) were recorded at 4, 6, 8, 10, 12, 24 and 48 h postoperatively.

The patients in Group N had decreased sufentanil consumption compared with those in Group R at 4–8 h, 8–12 h and 0–24 h after surgery ($P < 0.001$). There was no statistically significant difference between the two groups during the other time periods ($P > 0.05$). As shown in Supplementary Table 2 and Figure 4, the total consumption of sufentanil at 0–24 h after surgery was significantly reduced in Group N ($P < 0.001$).

There was no statistically significant difference in postoperative complications, time to first off-bed, time to first exhaust, length of hospital stay, or patient satisfaction between the two groups ($P > 0.05$, Table 2).

Discussion

This study investigated the use of nalbuphine as a ropivacaine adjuvant for ESPB in posterior lumbar surgery. The results demonstrated a substantial prolongation of time to first remedial analgesic request (approximately 98 minutes) with ropivacaine-nalbuphine versus ropivacaine alone for ESPB. Analgesic requirements were also markedly reduced over the initial 24 hours after surgery.

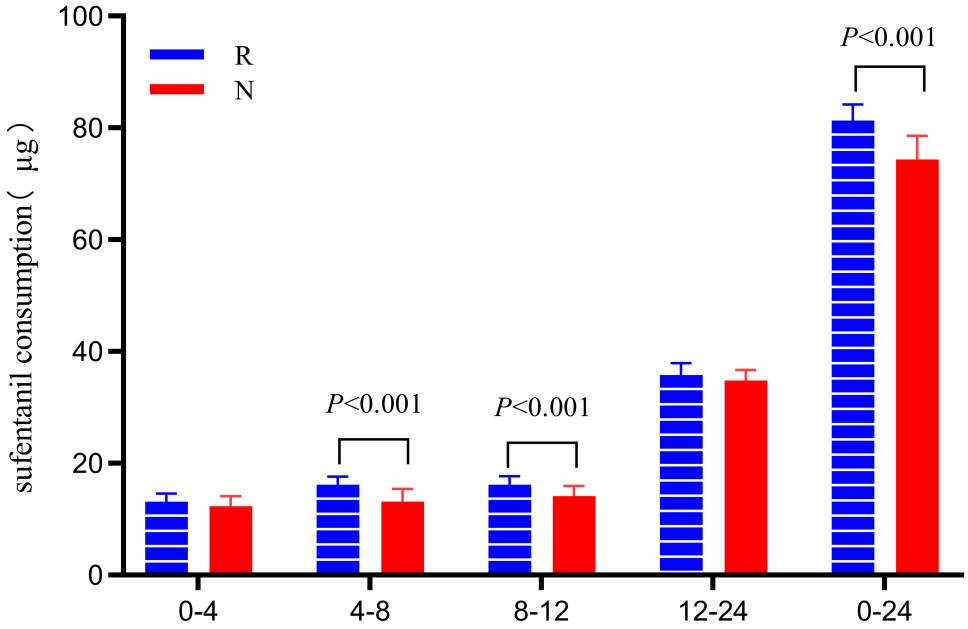

Figure 4 Cumulative sufentanil consumption in Group N and Group R at 0–4 h, 4–8 h, 8–12 h, 12–24 h and 0–24 h after surgery.

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Table 2 Postoperative Complications and Other Outcomes

	R (n=28)	N (n=29)	χ^2/ t	P
Nausea (n, %)†	7 (25.0)	3 (10.3)	1.223	0.269
Vomiting (n, %)†	5 (17.9)	5 (17.2)	0	1.000
Dizziness (n, %)†	4 (14.3)	3 (10.3)	0.002	0.960
Pruritus (n, %)†	3 (10.7)	2 (6.9)	0.002	0.967
Local anaesthetic systemic toxicity (n, %)†	0	0	–	–
SPO_2 < 93%§	1 (3.6)	0	–	0.491
First off-bed time ($\bar{x} \pm s$, h)*	82.43±6.00	80.69±6.77	1.025	0.310
First exhaust time ($\bar{x} \pm s$, h)*	8.57±1.43	8.67±1.37	0.266	0.822
Length of hospital stay ($\bar{x} \pm s$, d)*	8.68±1.42	8.55±1.35	0.346	0.731
Satisfaction situation (n, %)§			–	0.394
Not satisfied	3 (10.7)	2 (6.9)		
General satisfied	15 (53.6)	11 (37.9)		
Very satisfied	10 (35.7)	16 (55.2)		

Notes: *Independent sample *t*-test; †The χ^2 test; § Fisher's exact test. Values are presented as number (%) or mean ± standard deviation.

After surgery, especially internal fixation surgery, patients often suffer from severe pain. Inadequate pain control can lead to chronic pain development. Effective postoperative analgesia facilitates rehabilitation and expedited recovery following spinal trauma surgery. However, achieving satisfactory analgesia after spinal surgery remains challenging.

First described by Forero M et al in 2016,[1] ESPB provides a wide range of options for multimodal analgesia for spinal surgery. Zhu et al[3] reported that 20 mL of local anesthetic injected at the L_2 transverse process provided dermatomal analgesia spanning from T_8 to S_2; based on these findings, we targeted the transverse process at the surgical level for ESPB in this study. A meta-analysis of multiple studies showed that patients receiving ESPB have significantly lower postoperative pain scores, reduced consumption of opioid analgesics, decreased side effects such as nausea and vomiting, and earlier postoperative bed activity.[10–12]

As mentioned above, while single-injection local anesthetics have a limited duration, prolonging ESPB is critical for spinal surgery given the severity and persistence of postoperative pain. Multiple studies have demonstrated that peripheral opioid receptors increase in sensitivity after surgery and inflammation.[13–15] A systematic review and network Meta-analysis[16] confirmed that analgesic enhancement, prolonged duration, and intravenous opioid sparing occur when opioids (fentanyl, morphine, buprenorphine, etc.) are utilized as regional block adjuvants.

Nalbuphine is a derivative of 14-hydroxymorphine that has mixed κ receptor exciting effects and partial μ receptor antagonistic effects. Nalbuphine confers a robust, prolonged 3-6-hour analgesic effect. Intrathecal and epidural administration of nalbuphine prolongs sensory blockade and reduces analgesic demands.[17–19] The safe neuraxial application of peripheral blocks suggests their potential utility. Adjuvants such as nalbuphine blended with levobupivacaine for brachial plexus blockade[9] and bupivacaine for serratus plane blockade[20] have been shown to improve postoperative analgesia. The results of this study showed that the time to first remedial analgesic request was shorter than that in previous studies[9,20] because of more severe postoperative pain and greater demand for pain relief in lumbar trauma surgery, although there was a substantial prolongation of approximately 98 minutes with ropivacaine-nalbuphine versus ropivacaine alone for ESPB. NRS scores at rest and during movement in Group N were significantly lower than those in Group R (8 h, 10 h postoperatively), and sufentanil consumption was also reduced in Group N (4–8 h, 8–12 h and 0–-24 h postoperatively). This result demonstrated the application advantages of ropivacaine combined with nalbuphine for ESPB in lumbar trauma surgery. In our study, we used a total nalbuphine dose of 20 mg (10 mg per side) based on an optimal efficacy between 0.2–0.4 mg/kg[21,22] and a ceiling effect above 0.6 mg/kg. There was no significant difference in postoperative complications between the two groups in this study, suggesting that this nalbuphine dose is safe for ESPB. Furthermore, ultrasound-guided ESPB with 20 mg of nalbuphine added to ropivacaine improved the effect of analgesia and the sensory block duration for patients underwent percutaneous nephrolithotomy[23] or video-assisted thoracoscopic lobectomy surgery.[24]

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Our results demonstrated the superior analgesic efficacy of the addition of nalbuphine to ropivacaine for ESPB. The mechanisms underlying the enhancement of local anesthetic analgesia by nalbuphine remain incompletely elucidated but are likely multifactorial. It is speculated that 1) nalbuphine enhances postoperative analgesic effects through systemic absorption; 2) nalbuphine elicits analgesic effects by activating opioid receptors in the spinal cord and supraspinally through partial μ-receptor antagonism; 3) nalbuphine is activated by κ receptors that inhibit the release of pain neurotransmitters (substance P) and prolong the duration of analgesic effects;[25] and 4) as an adjuvant, nalbuphine alters the pH of local anesthetics, leading to an increase in potency and duration. The specific impact mechanism needs to be further studied.

There are several limitations in this study. First, the blood concentration of nalbuphine was not monitored, so it cannot be determined whether nalbuphine acts through systemic absorption or as a result of local blockade. Second, nalbuphine has a dose-dependent sedative effect, and this study did not utilize a sedative score; therefore, it is impossible to accurately evaluate whether the dosage of nalbuphine used was too high. Third, this study conducted ESPB after general anesthesia, so the range of sensory blockade areas could not be evaluated. Finally, the sample size of this study was calculated based on the time to first remedial analgesia, and it may be underpowered to accurately evaluate postoperative recovery and related side effects. Our results decisively demonstrated substantially augmented analgesia when nalbuphine was blended with ropivacaine for ESPB in spine surgery. These conclusions are applicable only to lumbar trauma surgery and may not be generalizable to other surgical procedures or patient populations.

Conclusion

For ESPB in posterior lumbar surgery, ropivacaine combined with nalbuphine significantly prolonged the duration of analgesia and reduced postoperative analgesic demands compared with ropivacaine alone.

Abbreviations

ESPB, Erector Spinae Plane Block; NRS, Numerical Rating Scale; PCA, Patient-controlled Analgesia; $ETCO_2$, End-expiratory Carbon Dioxide; MAP, Mean Arterial Pressure; SBP, Systolic Blood Pressure; PONV, Postoperative Nausea and Vomiting; PACU, Postanesthesia Care Unit; SpO_2, Peripheral Capillary Oxygen Saturation.

Data Sharing Statement

The raw data supporting the conclusions of this article will be made available. Further inquiries can be directly to the corresponding author.

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This paper has been uploaded to ResearchSquare as a preprint: https://www.researchsquare.com/article/rs-3504233/v1

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Disclosure

The authors declare that they have no conflicts of interest with regard to this work.

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