The Optimal Dosage of the Nalbuphine Preemptive Analgesia on Postoperative Pain in Patients Undergoing Laparoscopic Cholecystectomy: A Randomised, Controlled, Double-Blind Study

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ABSTRACT

Objective: To investigate the optimal dosage of nalbuphine preemptive analgesia on pain after laparoscopic cholecystectomy.
Study Design: A double-blind, randomised study.
Place and Duration of the Study: Department of Anaesthesiology, The Affiliated Huai'an Hospital of Xuzhou Medical University, Huai'an Second Hospital, Jiangsu Province, China, from 2020 to 2023.
Methodology: This study enrolled 240 patients requiring elective laparoscopic cholecystectomy. Patients were randomly allocated into four groups receiving placebo (Group NS) or nalbuphine 0.1 mg/kg (Group N1) or 0.2 mg/kg (Group N2) or 0.3 mg/kg (Group N3) intravenously 15 minutes before surgery. The postoperative visual analogue scale (VAS) score, and the rescue analgesic requirement within 72 hours after surgery were evaluated. One-way analysis of variance and a non-parametric Kruskal–Wallis test were used to compare differences between the groups.
Results: The VAS scores at rest and on movement were significantly lower in the N2 and N3 groups compared to the placebo group at 4, 12, 24, and 48 hours after surgery ($p < 0.05$). Moreover, the VAS scores of the N2 group were significantly lower than N1 and N3 groups. The first rescue analgesia time was significantly longer ($p < 0.05$), and the rescue analgesic requirements were considerably reduced in the N2 group than in the placebo group ($p < 0.05$).
Conclusion: Nalbuphine preemptive analgesia provided effective analgesia in patients undergoing laparoscopic cholecystectomy. The results showed that the optimal dose was 0.2 mg/kg for nalbuphine preemptive analgesia in laparoscopic cholecystectomy.

Key Words: *Nalbuphine, Preemptive analgesia, Laparoscopic cholecystectomy, Postoperative pain, Rescue analgesia, VAS score*.

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INTRODUCTION

Laparoscopic cholecystectomy is the mainstay treatment of benign biliary disease because of shorter hospital stays.[1] Compared with open cholecystectomy, postoperative pain following laparoscopic cholecystectomy tends to be less intense.[2,3] Nevertheless, pain is still an essential issue after laparoscopic cholecystectomy, which results in prolonged admissions or readmissions, late mobilisation, patient dissatisfaction, and chronic pain.[4-8]

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The incidence of pain after laparoscopic cholecystectomy was 63%.[9] Postoperative pain can be influenced by several factors, such as tissue injury from surgical trauma, nerve injury, and diaphragm irritation caused by leftover CO_2 pneumoperitoneum.[8,10,11] These factors lead to peritoneal irritation and central sensitisation. Therefore, effective anaesthetic medicines are needed for the prevention of pain after laparoscopic cholecystectomy.

Nalbuphine is classified as an opioid agonist-antagonist, and its analgesic effects are primarily achieved through its interactions with the μ and κ receptors in the body.[12] Nalbuphine has been specifically indicated for treating mild to moderate pain.[13] One of the significant features of nalbuphine is that it is less likely to cause side effects such as nausea and vomiting than other opioid analgesics.[14,15] Given these qualities, nalbuphine may be suitable for treating the complex pain associated with laparoscopic cholecystectomy. However, there is limited

evidence on the role and dose of nalbuphine in laparoscopic cholecystectomy. This study aimed to investigate the optimal dosage of nalbuphine preemptive analgesia in pain management after laparoscopic cholecystectomy and provide an evidence-based basis for optimising perioperative analgesia.

METHODOLOGY

The Hospital of Xuzhou Medical University's Ethics Committee approved this randomised controlled clinical trial on November 5, 2019 (Approval No: 28). The study was added to the Clinical Trial Registry on November 11, 2019. All patients enrolled in the study gave their informed consent.

Patients ≥18 years scheduled to have elective laparoscopic cholecystectomy surgery were eligible for this study, with the American Society of Anaesthesiologists Physical Status (ASA PS) classification of I–II and body-mass index (BMI) of less than 35 kg/m². Patients allergic to opioids, had serious problems with their liver or kidneys, or had serious heart issues were excluded from the study.

A power of 80% and a significance level (p-value) of 0.05 were used to determine the sample size. According to formal data from the department, in the placebo group, the average VAS score was 5.8 ± 4.2. It was expected that the nalbuphine group would show a big drop of 20%. For these reasons, a sample size of 51 people in each group was considered. In consideration of drop-outs, the authors assigned 60 patients to each group. Patients were randomly assigned to four groups. A statistician generated a list of random numbers, and an anaesthetist allocated each patient a randomisation number corresponding to their group. The patients and the attending physicians were blind to the group assignments. Another anaesthetist was responsible for collecting perioperative data. Until the completion of the assessment, no individual was informed about the group allocation. These patients were randomly assigned to the normal saline group (Group NS) and nalbuphine group (0.1 mg/kg, Group N1; 0.2 mg/kg, Group N2; 0.3 mg/kg group, Group N3). Study medicines were diluted with saline to 5 ml and given intravenously 15 minutes before surgery. The resident not involved in the study opened the sealed envelopes that contained the group allocation, while patients arrived in the operating room. On the evening before surgery, patients were introduced to a 10 cm linear visual analogue scale (VAS) for assessing their pain degree, with 0 representing no pain and 10 signifying the worst pain.

Patients fasted for 8 hours and did not drink water for 4 hours before surgery. A Philips Intellivue MP70 was used to monitor the heart rate (HR), peripheral oxygen saturation (SpO_2), end-tidal carbon dioxide pressure ($PETCO_2$), and an electrocardiogram (ECG) in the operating room. Besides the nalbuphine, no other medicine was given before the study. Nalbuphine (calculated by the pharmacist based on the patients' weight) was diluted with saline to 5 ml and given intravenously 15 minutes before surgery. All patients were given standard anaesthesia according to the protocol, which included midazolam 0.05 mg/kg, propofol 2 mg/kg, sufentanil 0.5 µg/kg, cisatracurium 0.15 mg/kg for induction of anaesthesia, keeping the end-tidal CO_2 level within 35 and 45 mmHg during surgery, and sevoflurane inhalation to keep the bispectral index between 40 and 60. Intermittent administration of cisatracurium 5 mg was performed for neuromuscular blockade. After surgery, atropine and neostigmine were administrated to restore muscle relaxation, then the tracheal tube was removed, and the authors continued to monitor the patients for at least 60 minutes in the post-anaesthesia care unit. The VAS scores of patients were assessed at rest and on movement (assessed by instructing the patient to take deep breaths or cough). If patients complained of pain, they received rescue analgesia with ketorolac tromethamine 30 mg intravenously, every 30 minutes until the VAS score was <3.

Data distribution was assessed using the Shapiro-Wilk's test. Age, weight, mean surgery duration, VAS scores, the first rescue analgesia time, and total rescue analgesic consumption were expressed as means and standard deviations or medians (interquartile range) as appropriate. One-way analysis of variance (ANOVA) was performed for comparisons between groups, and Bonferroni test was used for intergroup analysis. The authors used Chi-square or Fisher's exact tests to compare differences in gender. The non-parametric Kruskal–Wallis test was performed to compare the VAS scores, first rescue analgesia times, and total consumption of rescue analgesics. A post-hoc test was performed with Dunn's multiple test. A statistical significance level was set at $p < 0.05$. The statistical analysis was carried out with the help of GraphPad 9.0 (GraphPad, La Jolla, CA, USA).

RESULTS

The study screened 240 patients, and five were excluded (one was hypersensitive to anaesthetics, three did not meet the criteria, and one could not complete the study because of anaphylaxis). Two hundred and thirty-five patients were then randomly allocated to the Group NS, N1, N2, and N3. All enrolled patients completed this study. The baseline characteristics of the four groups were comparable concerning gender, body weight, age, height, and ASA PS. There were no differences in the duration of surgery or the total sufentanil amount used between the groups (Table I).

After surgery, the VAS scores were noted at 2, 4, 12, 24, 48, and 72 hours. Generally, the postoperative pain was higher at 12 hours, then decreased at 24, 48, and 72 hours in all groups (Figure 1A). At rest, the VAS scores showed significant differences among the four groups except at 2 hours. Compared with Group NS, the pain scores of Group N2 were greatly reduced at 2, 4, 12, 24, 48, and 72 hours postoperatively ($p = 0.015$, <0.001, <0.001, <0.001, <0.001, and <0.001, respectively), while they were substantially lower at 4, 12, 24, and 48 hours in Group N3 after the surgery ($p = 0.021$, 0.004, 0.011, and 0.011, respectively, Figure 1A). Additionally, in Group N2, the pain was considerably lower at 4, 12, 24, 48, and 72 hours than in Groups N1 ($p = 0.004$, <0.001, <0.001, <0.001, and <0.001, respectively), however, the pain degree in N1 and N3 groups were comparable (Figure 1A).

Table I: Demographics, baseline data, and surgery time.

Parameters	Group NS (n = 59)	Group N1 (n = 58)	Group N2 (n = 59)	Group N3 (n = 59)	p-value
Male / female	21/38	24/34	20/39	25/34	0.726
Age, years	51.24 ± 6.52	50.45 ± 6.22	46.76 ± 9.78	50.46 ± 10.24	0.017
Weight, kg	70 [65-70]	70 [64.7-80]	69 [60-75]	70 [64-75]	0.307
Height, cm	162 [160-165]	163.5 [158-169]	165 [162-167]	164 [157-167]	0.438
ASA PS, I:II	33/26	30/28	27/32	33/26	0.650
Duration of surgery, minutes	45 [30-65]	38 [31-62.5]	45 [35-55]	45 [30-70]	0.489
Intraoperative sufentanil, µg	35 [32-45]	39 [34-39]	35 [30-40]	35 [32-40]	0.435

ASA; American Society of Anaesthesiologists. One-way analysis of variance, Fisher's exact test, and Kruskal–Wallis test results were considered significant at p <0.05.

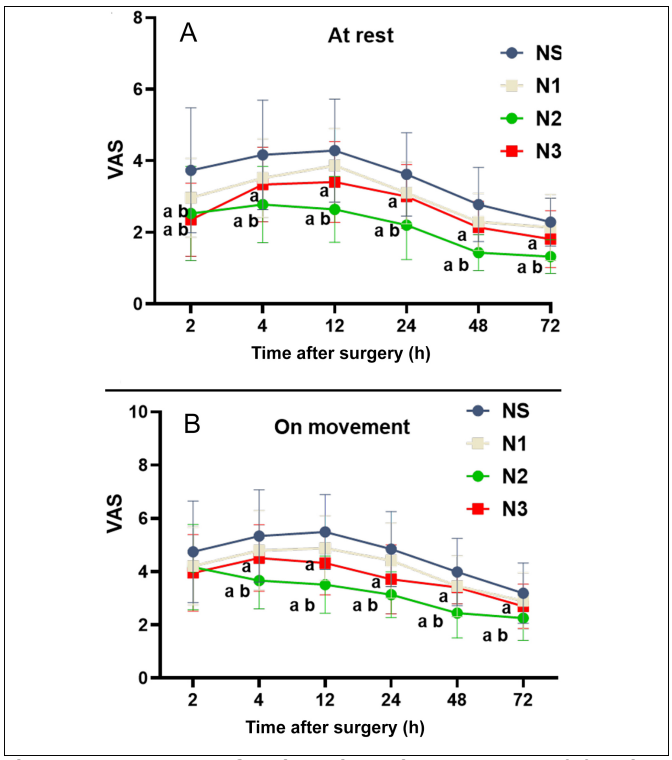

Figure 1: VAS scores of patients in each group at rest (A) and on movement (B).
VAS: Visual analogue scale. Kruskal–Wallis test results were considered significant at p <0.05. Compared with Group NS, [a]p <0.05, compared with Group N1, [b]p <0.05.

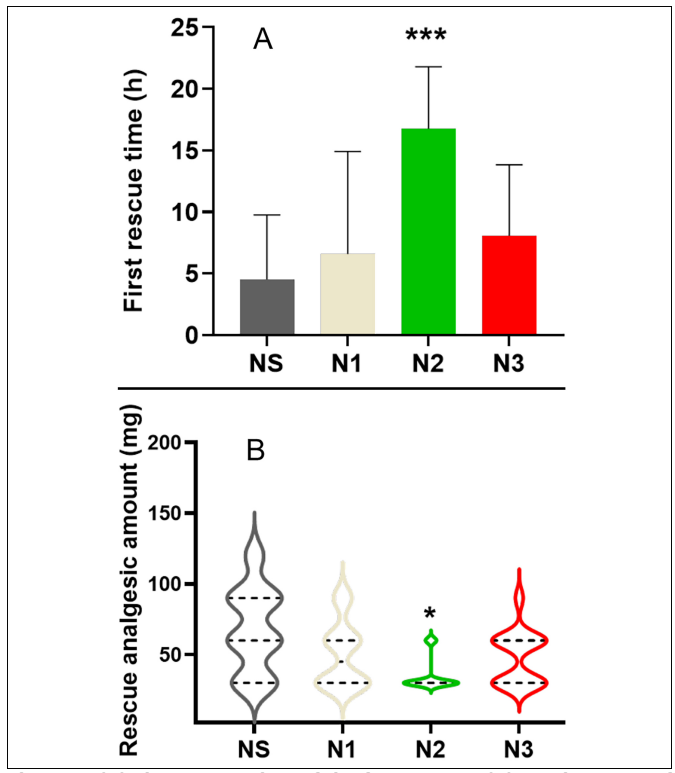

Figure 2: (A) First rescue time of the four groups. (B) Total amount of rescue analgesic of the four groups.
Kruskal–Wallis test results were considered significant at p <0.05. Compared with Group NS, *p <0.05.

On movement, there was a significant difference between groups in VAS scores except at 2 hours (p <0.001 for all). In comparison with Group NS, the pain scores on movement were significantly lower for time intervals of 4, 12, 24, 48, and 72 hours in Group N2 (p <0.001, <0.001, <0.001, <0.001, and <0.001, respectively), and the pain scores of Group N3 were lower at 4, 12, and 24 hours postoperatively (p = 0.025, <0.001, and <0.001, respectively, Figure 1B). Furthermore, at 4, 12, 24, 48, and 72 hours, the VAS scores for Group N2 were markedly lower compared to those observed in N1 and N3 groups (p = 0.001, <0.001, <0.001, <0.001, and = 0.002, respectively, Figure 1B). While Group N3 achieved superior VAS scores relative to Group N1, this difference did not reach statistical significance (Figure 1B).

The first rescue analgesia time was longer, and the total amount of rescue analgesia was less in N1 and N3 groups than in Group NS; however, the difference was not statistically significant (Figure 2A, B).

In Group N2, the first rescue analgesia time was significantly prolonged 2 (2-4) *vs*. 16 (12-22.5) h, (p <0.001), and the rescue analgesia requirement was lower than that of Group NS [60 mg (30-90) *vs*. 30 mg (30-37.5), p = 0.019, Figure 2A, B).

DISCUSSION

Laparoscopic surgery is a minimally invasive surgery. Nevertheless, patients still have a certain degree of pain after surgery because of intraoperative pneumoperitoneum, abdominal wall incision, and other things such as preoperative pain, perioperative mental state, and pain sensitivity. To alleviate the pain of patients, preemptive analgesia is used to lower the pain after surgery and the number of analgesic consumptions.[16]

Nalbuphine is one of the candidates for preemptive analgesia, which offers adequate postoperative analgesia and sedation.[17,18] Using nalbuphine and dexmedetomidine as

preemptive analgesia during endoscopic sinus surgery cannot only stabilise the patients' blood pressure, but it can also lower the amount of anaesthetic during the surgery, ease pain afterwards, and improve the recovery quality.[14] Another study showed that nalbuphine reduced postoperative shivering incidence, and decreased analgesia requirements than ketorolac in patients who received surgery under spinal anaesthesia.[19] In this study, patients receiving nalbuphine 0.2 mg/kg and 0.3 mg/kg had less pain at rest and on movement than the control condition at 4, 12, 24, and 48 hours postoperatively. In Group N2, the VAS scores were much lower than those for the other groups, suggesting that nalbuphine 0.2 mg/kg had a better analgesic effect. The result also indicated that nalbuphine 0.2 mg/kg showed better analgesia effects than 0.3 mg/kg, partly because mixed agonists/antagonists may act as agonists at low doses and as antagonists at higher doses.[20] Recent studies found that nalbuphine not only produced analgesic effects but also had anti-analgesic effects, when combined with the pure μ-opioid receptor at various dose ratios, it exerts enhanced analgesia or diminished analgesic effects. Another explanation for the weak anti-analgesic effect of nalbuphine 0.3 mg/kg may have been related to the high dosage of sufentanil used during anaesthesia induction.

Kumari *et al*. reported that the combination of nalbuphine with intrathecal bupivacaine extended analgesic duration, reduced rescue analgesic doses, and accelerated the onset of sensory block.[21] Huang *et al*. reported that the addition of nalbuphine to ropivacaine in an ultrasound-guided fascia iliac compartment block resulted in extended analgesic duration, reduced pain levels, and decreased the need for parecoxib sodium rescue medication among elderly patients following a hip fracture while demonstrating minimal side effects.[22] A recent prospective study indicated that nalbuphine displayed an analgesic effect comparable to that of morphine, while also showing greatly reduced rates of postoperative respiratory depression, itching, and postoperative nausea and vomiting in children undergoing laparoscopic surgery.[23] In the present study, the first rescue analgesia time was significantly prolonged and the total amount of rescue analgesia was lowered in Group N2, suggesting that nalbuphine 0.2 mg/kg effectively alleviated postoperative pain and minimised analgesic consumption. Another study found that nalbuphine greatly decreased pain after surgery and the need for fentanyl, and it also delayed the first request for pain medication, a result consistent with those of the present study.[24] Additionally, in this study, no patient experienced from deep sedation as the sedative effect of nalbuphine is dosage-related, and it shows the most substantial sedative effect at 0.4 mg/kg.[25]

This study has several limitations. First, different types of opioids were used in this research, and problematic medicine interactions among opioids (nalbuphine and sufentanil) could influence the results. Different dosage ratios may exhibit other effects, and further studies are needed to explore the optimal balance. Second, the study considered only those patients who underwent laparoscopic cholecystectomy, and these findings cannot be generalised to other types of surgeries. Finally, as a single-centre study with a relatively small number of patients, the generalisability of findings should be corroborated in larger multicentre trials.

CONCLUSION

This study showed that nalbuphine preemptive analgesia effectively alleviates pain after laparoscopic cholecystectomy, and the optimal dose was 0.2 mg/kg for preemptive analgesia using nalbuphine.

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ETHICAL APPROVAL:
Ethical approval for this study was granted by the Institutional Review Board of the Affiliated Huai'an Hospital of Xuzhou Medical University (Registration No: HEYLL201928; Date of the Approval: 5 November 2019).

PATIENTS' CONSENT:
Written informed consent was provided by the patients.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
PC: Concept, literature, and drafting of the manuscript.
HW: Design, analysis, interpretation, literature review, report writing, and data collection.
DL, XJ: Acquisition and drafting of the manuscript.
All authors approved the final version of the manuscript to be published.

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