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ORIGINAL RESEARCH

Preemptive Intravenous Nalbuphine for the Treatment of Post-Operative Visceral Pain: A Multicenter, Double-Blind, Placebo-Controlled, Randomized Clinical Trial

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ABSTRACT

Introduction: Post-operative visceral pain is common in early postoperative period after laparoscopic surgery. As a kappa opioid receptor agonist, the antinociceptive effects of nalbuphine in visceral pain are consistent across a multitude of experimental conditions irrespective of species. We hypothesized that preemptive nalbuphine can decrease the visceral pain for patients with incisional infiltration of ropivacaine after laparoscopic cholecystectomy.

Methods: In a multicenter, prospective, double-blind, placebo-controlled, randomized clinical trial, 2094 participants scheduled for laparoscopic cholecystectomy were randomly assigned to receive nalbuphine (Nal group, $n = 1029$) or placebo (Con group, $n = 1027$). The Nal group received intravenous nalbuphine 0.2 $mg \cdot kg^{-1}$ and the Con group received saline in a similar way. The primary endpoint was the effect of nalbuphine on post-operative visceral pain intensity scores within 24 h postoperatively. The total amount of analgesic as well as complications were recorded.

Results: A total of 1934 participants were analyzed. Nalbuphine reduced the visceral pain both at rest ($\beta = -0.1189$, 95% CI -0.23 to -0.01, $P = 0.037$) and movement ($\beta = -0.1076$, 95% CI -0.21 to -0.01, $P = 0.040$) compared with placebo. Patients in the Nal group required less frequent supplemental analgesic administration during the first 24 h after surgery. There were fewer patients in the Nal group who experienced nausea and vomiting (PONV) ($P = 0.008$).

Conclusions: Preemptive nalbuphine administered at a dose of 0.2 $mg \cdot kg^{-1}$ was safe and effective at reducing the postoperative visceral pain and supplemental analgesic use in patients undergoing laparoscopic cholecystectomy.

Trial Registration: Chinese Clinical Trial Registry; ChiCTR1800014379.

Keywords: Laparoscopy; Cholecystectomy; Postoperative; Pain; Opioids

Xiaofen Liu and Jun Hu contributed equally to this work.

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Key Summary Points

Why carry out this study?

Laparoscopic cholecystectomy is one of the most frequently performed operations worldwide, nevertheless the majority of the patients suffer from visceral pain in the early period after surgery.

Nalbuphine is an inexpensive, non-controlled, opioid analgesic that has been in clinical use for decades. As both a kappa opioid receptor agonist and mu opioid receptor antagonist, it exhibits greater effectiveness against visceral pain than morphine in preclinical research.

We hypothesized that nalbuphine could reduce the postoperative visceral pain and supplemental analgesic use in patients undergoing laparoscopic cholecystectomy.

What was learned from the study?

Preemptive nalbuphine administered at a dose of 0.2 $mg{\cdot}kg^{-1}$ was safe and effective at reducing the postoperative visceral pain and supplemental analgesic use in patients undergoing laparoscopic cholecystectomy.

Preemptive nalbuphine also improved sleep quality and post-operative nausea and vomiting (PONV) without any adverse effects.

Preemptive nalbuphine exhibited a better visceral pain relief post-surgery for patients with symptomatic gallbladder disease longer than 6 months.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14610237.

INTRODUCTION

Cholecystectomy is one of the most frequently performed operations. Laparoscopic cholecystectomy was introduced in the 1980s and rapidly became the method of choice for removal of the gallbladder. This rising popularity was based on many benefits, such as reduced tissue trauma, rapid recovery, and shorter hospital stay with cheaper health costs compared with open surgery. It has been accepted worldwide as a well-established intervention for gallbladder disease [1].

Post-operative pain continues to be an important issue after laparoscopic cholecystectomy and can contribute to prolonged in-hospital stay and readmission [2]. A review of earlier data showed that pain is most severe on the day of surgery [3, 4]. The nature of acute pain post laparoscopic cholecystectomy is complicated, including components of incisional, non-localized visceral, and referred shoulder pain [5]. Joris et al. have shown that visceral pain accounts for most of the discomfort experienced in the early postoperative period with the incisional component being less intense owing to the small incisions causing limited damage to the abdominal wall [6]. Post-operative visceral pain is particularly prominent because of organ injury and peritoneal inflammation, regional acidosis, and visceral mucosal tissue ischemia induced by elevated intraperitoneal pressure from pneumoperitoneum [5]. Furthermore, higher visceral pain in the first post-operative week is an independent predictor for chronic unexplained pain at 12 months, posing a burden on both society and the individual patient [7].

The likely development of peritoneal inflammation after pneumoperitoneum provides a rationale for the use of nonsteroidal anti-inflammatory drugs (NSAIDs) [8]. However, treatment of post laparoscopy pain with NSAIDs yields equivocal results [9, 10]. Further, because of the pathophysiologic changes in renal blood flow induced by pneumoperitoneum, the safety

of preoperative NSAIDs use must be considered [11]. The analgesic effects of intraperitoneal local anesthetics have also been investigated by several controlled studies with little showing benefits from preemptive analgesia compared with postoperative analgesic treatment [12–14].

Opioids remain one of the most common medications used by anesthesiologists to treat moderate to severe pain. Nalbuphine is a non-controlled, inexpensive, opioid analgesic which has been used clinically for decades. Nalbuphine has been proven to relieve both visceral and somatic pain in mouse analgesiometric studies [15–18]. Furthermore, it is more potent for visceral pain than somatic pain with an ED50 (0.44 mg kg^{-1}) in abdominal constriction response induced by acetic acid in mice [16]. Nalbuphine agonize the kappa receptor and antagonize the mu receptor. The use of mu antagonist/kappa agonists can be instrumental in partially antagonizing untoward effects caused by pure mu opioids. Given these qualities, it may be suitable for treating the complex pain associated with laparoscopic cholecystectomy. Therefore, we performed a multicenter large-scale clinical trial to specifically assess the efficacy and safety of preemptive nalbuphine on the visceral pain for patients combined ropivacaine injections at laparoscopic port sites after cholecystectomy.

METHODS

Study Design and Participants

This was a multi-center, randomized, double-blind, parallel-group, placebo-controlled trial. It was conducted at 16 hospitals in China from February 2018 to December 2018 enrolling 2094 participants and evaluated the safety and efficacy of a single intravenous dose of 0.2 mg·kg^{-1} nalbuphine before surgery against placebo on patient post-operative visceral pain after laparoscopic cholecystectomy. This study was approved by the The Second Hospital of Anhui Medical University's Ethics committee (YJ-YX2017-018). The study was in accordance with the Declaration of Helsinki and its later amendments. The trial was registered prior to patient enrolment at Chinese Clinical Trial Registry (http://www.chictr.org.cn, Registration No. ChiCTR1800014379, Principal investigator: Ye Zhang, Date of registration: 2018-01-09). All patients signed the written informed consent form.

Adult patients undergoing elective laparoscopic cholecystectomy, between the ages of 18 and 65 years, American Society of Anesthesiologists (ASA) classes I–II and with ability to consent, were approached at the preoperative assessment, clinic, or upon admission for surgery. Once eligibility has been confirmed, informed consent was sought. Exclusion criteria included: a history of any long-term drug abuse; any known adverse reaction to nalbuphine; known significant liver or kidney dysfunction; pregnant or lactating women; and body mass index (BMI) > 30 kg·m^{-2}.

Randomization and Blinding

Participants were randomly assigned 1:1 between nalbuphine (Nal) and placebo (Con) with permuted blocks (block size of four). Random assignment was administered at the Clinical Trials Centre of The Second Hospital of Anhui Medical University by a computerized random number generator. The detailed information of the group assignment was contained in a sequentially numbered, opaque sealed envelope prepared by a statistician. The sequence of randomization was stratified according to medical center. Treatment allocation was unmasked. The administration of nalbuphine was recoded only on the specific form by the anesthetist. To avoid any bias in postoperative rescue analgesic administration, the anesthetist is asked not to be involved in the postoperative pain evaluation and management.

Interventions

Study drugs (nalbuphine 20 mg·2 ml^{-1} and normal saline 2 ml) were offered as clear aqueous solutions in identical bottles (manufactured by Yichang Renfu Pharmaceutical Co., Ltd., Yichang, China) and dispensed according to the

treatment allocation results. The study drugs were diluted with normal saline to 50 ml (i.e., nalbuphine final concentration was 0.4 $mg \cdot ml^{-1}$) before administration. All study drugs were administered before skin incision and were given as a continuous intravenous infusion at a rate of 3 $ml \cdot kg^{-1}$ per hour for 10 min (0.2 $mg \cdot kg^{-1}$) intravenous nalbuphine in the treatment group. Before skin closure, all patients received 10 ml 0.5% ropivacaine injected into the skin, subcutaneous tissue, and muscle fascia at each of the laparoscopic port sites. No further post-operative pain control measures were conducted during the operation. All operations were performed from 8 a.m. to 4 p.m. Postoperative rescue analgesic in the form of sufentanil bolus of 5 μg was administered intravenously at the request of the patient and the evaluation by the post-operative pain if VAS $\geq$ 4 and it could be repeated every 10 min until VAS $\leq$ 3. The treating anesthesiologists were not involved in the postoperative care other than in exceptional circumstances for medical emergencies in the acute postoperative period. Nalbuphine was not prescribed within the first postoperative 48 h for participants in either arm.

Anesthetic and Surgical Procedure Protocol

All the patients routinely had peripheral venous catheter access in the upper extremity and were monitored for the electrocardiogram changes, heart rate, oxygen saturation, blood pressure, and bispectral index (BIS). Anesthesia was maintained with total intravenous anesthesia (TIVA) by propofol and remifentanil. Furthermore, sufentanil was used for induction only and remifentanil for maintenance of anesthesia to keep the type of opioid consistent. Anesthesia was induced by intravenous injection of sufentanil (0.5 $\mu g \cdot kg^{-1}$), propofol (2–-3 $mg \cdot kg^{-1}$), and neuromuscular blocking agents were used as per preference of the anesthesiologist. Following endotracheal intubation, anesthesia was maintained with propofol (4–8 $mg \cdot kg^{-1} \cdot h^{-1}$) and remifentanil (0.1–-0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Intra-operatively, BIS values were maintained within 45 $\pm$ 5 by regulating the administration rate of propofol and remifentanil. The procedure was routinely performed with three ports located in the umbilicus, under the xiphoid and the midline of the clavicle [19]. A laparoscope was placed through the umbilical port, and the grasping forceps were placed in the xiphoid incision and the midline of the clavicle incision. Carbon dioxide (CO_2) pneumoperitoneum pressure was set at 12–14 mmHg (1 mmHg = 0.133 kPa). About 20 min before the end of the surgery, granisetron (3 mg) and dexamethasone (10 mg) were given to prevent nausea and vomiting. Propofol and remifentanil were discontinued at the time of wound closure. The endotracheal tube was removed after the patient regained full consciousness.

Outcome Measures

The primary outcome measured was the post-operative visceral pain intensity scores within 24 h postoperatively. Before surgery, the patients were instructed to use a 100-mm Visual Analog Scale (VAS) [0–10, 0 = no pain, 1–-3 = mild pain, 4–6 = moderate pain, 7–-10 = severe pain, 10 = worst pain imaginable] to rate the following three pain components: incisional pain (somatic pain component) was defined as a superficial pain, wound pain, or pain located in the abdominal wall, a pain that one can "touch." Visceral pain (intraabdominal pain component) was defined as pain inside the abdomen, which may be deep, dull, and more difficult to localize, and may resemble a biliary pain attack. Shoulder pain (referred pain component) was defined as a sensation of pain in the shoulder [20]. The degree of incision pain and visceral pain were evaluated when rest and movement (cough and deep breathing) respectively. Each patient was supplied with a questionnaire consisting of VAS score forms. Follow-up evaluations were conducted at 1 (T1), 2 (T2), 4 (T3), 8 (T4), 12 (T5), 16 (T6), 20 (T7), and 24 (T8) hours after surgery by anesthesiologists blinded to grouping and asked the patients the same questions. Sufentanil (5 μg) boluses was administered as rescue analgesic if VAS $\geq$ 4 and

it could be repeated every 10 min until VAS ≤ 3, and the number of rescue analgesic boluses was recorded. Postoperative complications were also recorded. Besides, post-operative quality of sleep (sleep quality was evaluated on a scale of 0 to 10 [0, bad sleep; 10, excellent sleep] at 7:00 a.m. on the next morning of surgery) and the patients' satisfaction were documented with four levels (Very satisfied, Satisfied, Neutral, Dissatisfied). Postoperative complications were also recorded.

Statistical Analysis

The sample size calculation for this trial was based on our preliminary study on 40 patients who had undergone laparoscopic cholecystectomy between December 2017 and January 2018. The sample sizes of 860 per arm was based on 90% power and two-sided significance testing at the $\alpha = 0.01$ level to detect a difference of 0.3 points on VAS for visceral pain at rest in a design with eight repeated measurements having a compound symmetry covariance structure when the standard deviation is 2, the correlation between observations on the same subject is 0.7. We expected a dropout rate of about 20%. The number of patients to be included was calculated as 2094 (1047 in each arm). Continuous data were tested for normal distribution by the Kolmogorov–Smirnov test. Normally distributed data were expressed as mean ± standard deviation ($\overline{x} \pm s$), non-normally distributed data were presented as median (inter-quartile range), and categorical data were shown as numbers (percentages). We used t tests for continuous variables and χ^2 tests for categorical variables. The primary endpoint VAS scores at the various time points between the two groups were compared using generalized linear mixed model (GLMM) for repeated measures, which allowed us to control for potential confounders (i.e., gender, BMI, and pneumoperitoneum pressure). Treatment effect estimates for comparing each time point between groups were calculated with LSD correction. Since this trial was designed as an effectiveness investigation, per-protocol analyses (PPA) were performed, which only included participants who completed the investigation. All statistical analyses were carried out by using SPSS 23.0 software (IBM, Armonk, NY, USA). A P value < 0.05 was considered statistically significant.

RESULTS

Study Population

From February 2018 to December 2018, we approached 2094 eligible participants from the 16 sites and 38 declined to participate, leaving 1029 patients randomly allocated to receive nalbuphine (Nal) and 1027 to placebo (Con). A failure to complete laparoscopic cholecystectomy according the procedural or anesthesia protocol occurred in 31 and 24 participants, respectively, with seven participants failing to finish the questionnaire forms in the nalbuphine group. Similarly, 28 and 22 participants were excluded due to procedural or anesthesia protocol violations with ten participants failing to finish the questionnaire from the placebo arm. A total of 1934 patients completed the study and were eventually considered in the analysis (Fig. 1).

Patient demographics, anesthetic agents, and duration of surgery were similarly between treatment groups (Tables 1, 2).

Pain Reduction

Following adjustments for gender, BMI, and pneumoperitoneum pressure, we found a treatment effect for the visceral pain in Nal group both at rest ($\beta = -0.1189$, 95% CI -0.23 to -0.01, $P = 0.037$) and movement ($\beta = -0.1076$, 95% CI -0.21 to -0.01, $P = 0.040$) vs. the Con group (Table 3). However, no treatment effect was found for the incisional pain at both rest ($\beta = -0.0084$, 95% CI -0.10 to -0.08, $P = 0.858$) and movement ($\beta = -0.0084$, 95% CI -0.10 to -0.08, $P = 0.857$), as well as shoulder pain ($\beta = 0.0242$, 95% CI -0.03 to 0.07, $P = 0.337$) among the two groups (Table 3). In further analysis, we found that nalbuphine can ameliorate visceral

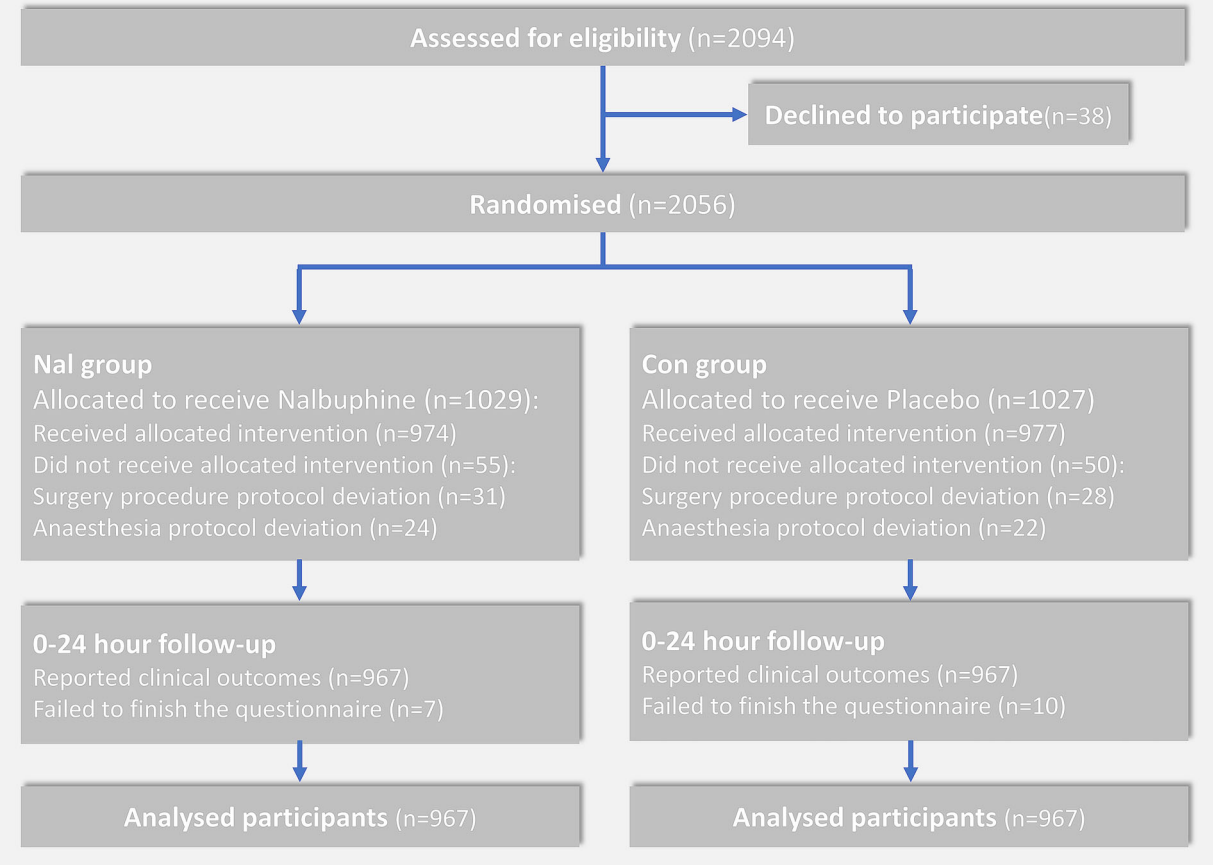

Fig. 1 CONSORT diagram of patient flow

pain both at rest and movement during T1, T2, T3, and T4 (all $P < 0.001$, Fig. 2). Besides, nalbuphine also decreased incisional pain in movement at T3 and T4 ($P < 0.001$, Fig. 2) due to the interaction of treatment and time effects for incisional pain in two groups ($P < 0.05$). Importantly, participants in the Nal group required less frequent supplemental analgesic administration during the first 24 h after surgery ($P < 0.001$, Fig. 3 and Table 4). In subgroup analysis, we found that as the history of symptomatic gallbladder disease prolonged, the visceral pain at rest after surgery gradually increased. Accidentally, for patients with a history of symptomatic gallbladder disease more than 6 months, the VAS of visceral pain at rest peaked 4.4 ± 1.8 at T1 in the Con group, while the VAS of the nalbuphine group was only 2.4 ± 2.5, with a significant decrease at the same timepoint ($P = 0.004$, Fig. 4).

Sleep and PONV Improvement

Administration of nalbuphine obviously improved sleep quality with a higher subjective sleep quality compared with the Con group at night of surgery ($P < 0.001$, Fig. 5). There was no significant difference in the patients' satisfaction between the two groups ($P = 0.233$, Table 4). There were fewer patients in the Nal group who experienced post-operative nausea and vomiting (PONV) (Nal = 195 [20.2%] vs. Con = 244 [25.2%], $P = 0.008$, Table 5).

Safety Outcomes

There was no significant difference in the incidence of other adverse events between the two

Table 1 Baseline characteristics

	Nal group (n = 967)	Con group (n = 967)	P
Male sex	353 (36.5%)	338 (35.0%)	0.477
Age (years)	46.7 ± 10.6	46.2 ± 10.7	0.307
BMI ($kg \cdot m^{-2}$)	24.0 ± 2.7	24.0 ± 2.8	0.955
Diagnosis			
Cholecystolithiasis	940 (97.2%)	940 (97.2%)	0.603
Chronic cholecystitis	7 (0.7%)	10 (1.0%)	
Gallbladder polyps	16 (1.7%)	11 (1.1%)	
Other	4 (0.4%)	6 (0.6%)	
Comorbidity			
Hypertension	103 (10.7%)	85 (8.8%)	0.167
Diabetes	45 (4.7%)	33 (3.4%)	0.165
Heart disease	12 (1.2%)	8 (0.8%)	0.369
Respiratory disease	11 (1.1%)	10 (1.0%)	0.826
Other comorbidities	60 (6.2%)	49 (5.1%)	0.278
Smoking	139 (14.4%)	135 (14.0%)	0.794
Alcohol drinking	31 (3.2%)	32 (3.3%)	0.898
Duration of symptomatic gallbladder disease			
Asymptomatic	43 (4.4%)	47 (4.9%)	0.674
< 3 months	782 (80.9%)	789 (81.6%)	
3–6 months	119 (12.3%)	104 (10.8%)	
> 6 months	23 (2.4%)	27 (2.7%)	
ASA classification			
I	822 (85.0%)	851 (88.0%)	0.054
II	145 (15.0%)	116 (12.0%)	

Data are presented as mean ± standard deviation or number (%)
BMI body mass index, *ASA* American Society of Anesthesiologists, *MAP* mean arterial pressure, *HR* heart rate

groups, apart from a statistically significant delay in regaining consciousness (P = 0.003) and extubation in the Nal group (P = 0.036, Table 5).

DISCUSSION

This multicenter large-scale randomized parallel trial demonstrated that a simple perioperative administration of nalbuphine significantly decreased early postoperative visceral pain for patients undergoing laparoscopic

Table 2 Intraoperative data

	Nal group (n = 967)	Con group (n = 967)	P
Duration of surgery (min)	49.6 ± 21.4	47.8 ± 21.5	0.064
Anesthesia time (min)	64.2 ± 23.2	62.3 ± 23.3	0.066
Dose of anesthetics			
Sufentanil (μg)	32.2 ± 4.9	32.1 ± 5.3	0.766
Propofol (mg)	377.9 ± 128.2	367.8 ± 128.0	0.083
Remifentanil (μg)	1014.4 ± 468.9	974.1 ± 457.7	0.056
Total fluid infusion (ml)	389.1 ± 153.6	377.3 ± 149.2	0.088
Estimated blood loss (ml)	14.0 ± 8.2	13.3 ± 18.0	0.259

Results are presented as mean ± standard deviation

Table 3 Postoperative pain between Nal vs. Con in generalized linear mixed model (GLMM)

	β	Between-group difference (95% CI)	P
Visceral pain at movement	− 0.1076	− 0.21 to − 0.01	0.040
Visceral pain at rest	− 0.1189	− 0.23 to − 0.01	0.037
Incision pain at movement	− 0.0084	− 0.10 to 0.08	0.857
Incision pain at rest	− 0.0084	− 0.10 to 0.08	0.858
Shoulder pain	0.0242	− 0.03 to 0.07	0.337

CI confidence interval

cholecystectomy during the first 8 h and led to a lower analgesic requirement in the first 24 h after surgery. Interestingly, for patients with symptomatic gallbladder disease longer than 6 months, preemptive nalbuphine significantly decreased the visceral pain from 4.4 to 2.4 in first hour post-surgery. However, there were no effects on the referred shoulder or incisional pain between the two groups.

Parenteral nalbuphine readily crosses the blood–brain barrier, takes effect about 2 min after administration, and reaches peak serum level after 5 min, and the action ranges from 2 to 6 h [21]. Systemic κ-agonists act as particularly effective analgesics in a wide variety of preclinical visceral pain models [22, 23]. The analgesic effects of κ-agonists in visceral pain are consistent across a multitude of conditions irrespective of species (rats or mice), treated visceral organs (gallbladder, stomach, intestine, colon, or peritoneum), nature of noxious stimuli (chemical irritant or distension), anesthetized or conscious animals, basal or inflammatory pain [24]. Overall, these properties are expected to arouse interest in the therapeutic effects of nalbuphine under various conditions with visceral pain and postoperative pain after abdominal surgery. The data in this study showed that the visceral pain increased progressively in the first 8 h after surgery in the control arm, and preemptive nalbuphine decreased this pain component at 1–8 h postoperatively. In line with our results, Lenz et al. also reported that patients suffer severe visceral

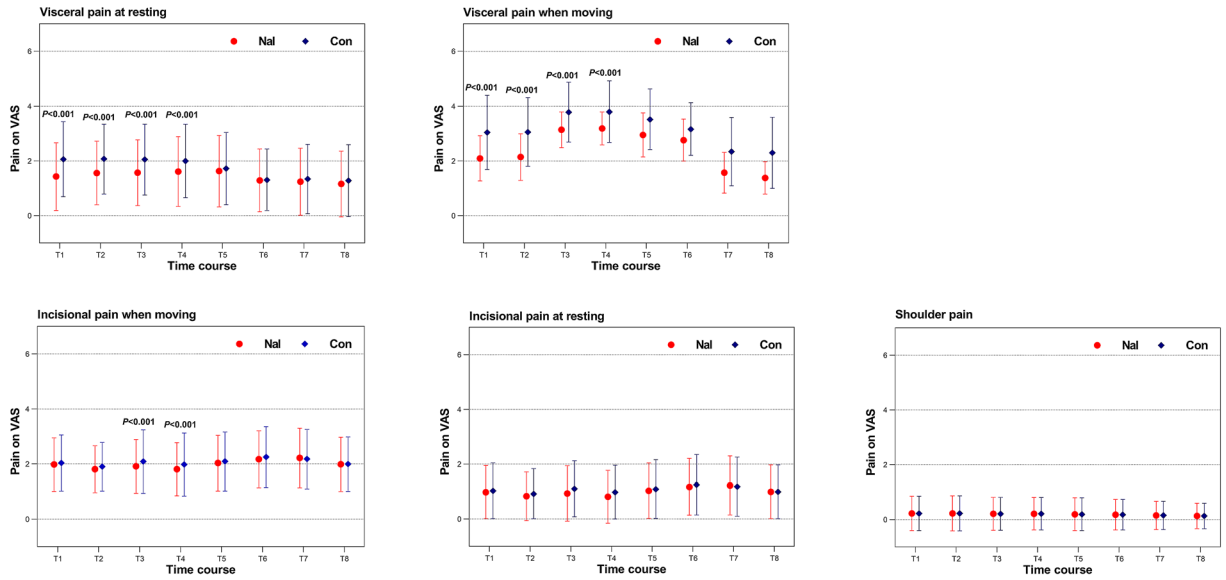

Fig. 2 Pain intensity scores for all time points throughout the study. *Nal* Nalbuphine, *Con* control, *VAS* Visual Analog Scale

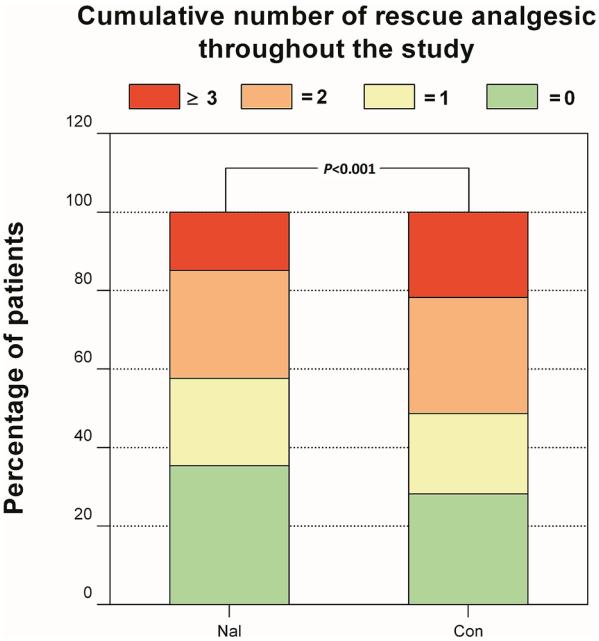

Fig. 3 Cumulative number of rescue analgesic throughout the study. *Nal* Nalbuphine, *Con* control

Table 4 Cumulative number of rescue analgesic and the patients' satisfaction within 24 h after the surgery

	Nal group (n = 967)	Con group (n = 967)	P
Cumulative number of rescue analgesic			
0	342 (35.4%)	273 (28.2%)	< 0.001
1	216 (22.3%)	198 (20.5%)	
2	265 (27.4%)	285 (29.5%)	
≥ 3	144 (14.9%)	211 (21.8%)	
Satisfaction			
Very satisfied	220 (22.8%)	197 (20.4%)	0.233
Satisfied	594 (61.4%)	586 (60.6%)	
Neutral	142 (14.7%)	169 (17.5%)	
Dissatisfied	11 (1.1%)	15 (1.6%)	

Data are presented as number (%)

pain between 2 and 8 h after laparoscopic surgery [25]. However, the analgesic advantage of nalbuphine did not last for more than 8 h after surgery, regardless of whether a single dose or its action ranges no more than 8 h. A possible explanation is that the pain elicited by this type of minimally invasive surgery was too low to yield a significant difference in pain scores at 48 h after surgery [26]. It is interesting that in our subgroup analyses, we found that patients with a history of symptomatic gallbladder

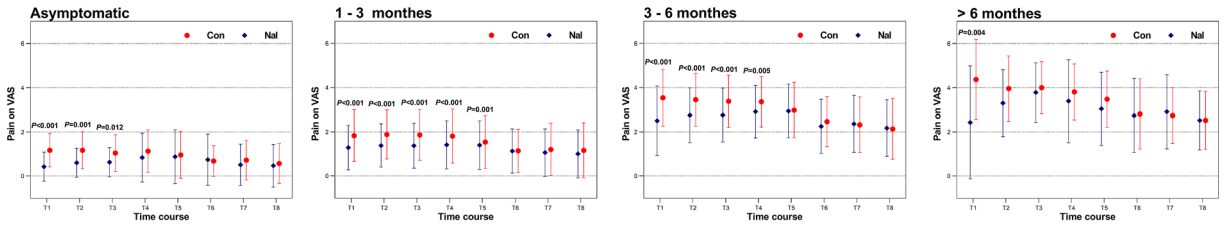

Fig. 4 Visceral pain intensity scores at rest for patients with different durations of symptomatic gallbladder disease before surgery. *Nal* Nalbuphine, *Con* control, *VAS* Visual Analog Scale

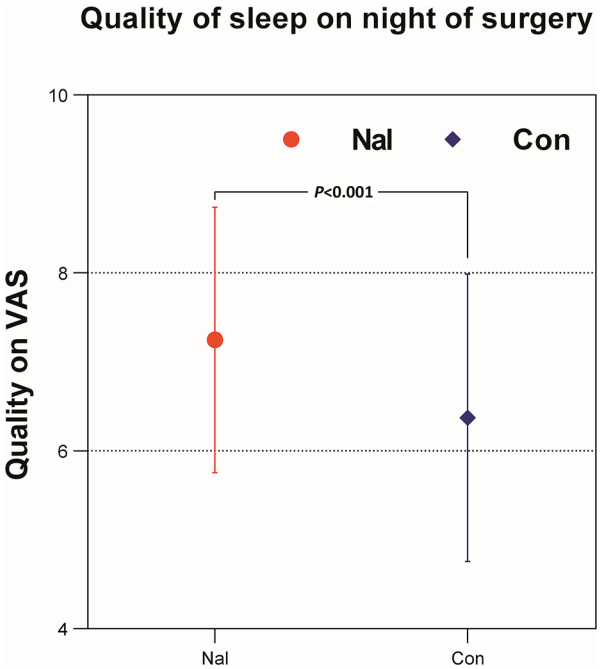

Fig. 5 Quality of sleep. *Nal* Nalbuphine, *Con* control, *VAS* Visual Analog Scale

disease longer than 6 months at baseline is more likely to be visceral pain relief by preemptive nalbuphine. Prolonged symptomatic gallbladder disease presents a chronic condition caused by continuous inflammation. The inflammation-induced hyperexcitability of extrinsic visceral afferents is associated with nociceptive and opioid receptors [27], which are related to potentiation of hypersensitivity and hyperalgesia [28]. The results were unexpected; to the best of our knowledge, there is no report about the effect of nalbuphine on visceral hyperalgesia, although we have reported that nalbuphine can improve remifentanil-induced hyperalgesia (RIH) [29]. Perhaps the results of the current study can provide some hints for future investigation of nalbuphine in this scenario.

In contrast to the positive findings for visceral and incisional pain, we failed to find any beneficial effect of nalbuphine for post-laparoscopic shoulder pain, a relatively common and distressing symptom. Several mechanisms have been attributed to the development of this symptom, with distension-induced neurapraxia of the phrenic nerve during pneumoperitoneum being considered as the most likely cause [30]. The phrenic nerve is composed primarily of the anterior branch of the C4 spinal nerve root, which also provides cutaneous innervation for the shoulder. Therefore, irritation of the diaphragmatic surface during laparoscopic procedures may generate nociceptive impulses that are conducted via the phrenic nerve and referred to the shoulder. The severity of this shoulder pain was typically less in the immediate post-op period, but increased to a maximum at around 24 h. This pattern is not a good match for the pharmacokinetic profile of the single bolus of preemptive nalbuphine that was used in this study and may explain its lack of efficacy for this pain. Although we found that nalbuphine can improve visceral pain after surgery, there was no significant difference in patient satisfaction with postoperative pain management between the two groups. This may be due to our meticulous postoperative follow-up and timely remedial analgesia. A recent RCT study also showed that multimodal drug analgesia can improve postoperative pain, but there was no significant improvement in patient satisfaction [31].

It is worth noting that patients in the nalbuphine group had better quality of sleep than

Table 5 Comparing the incidence of adverse events within 24 h after the surgery

	Nal group (n = 967)	Con group (n = 967)	P
PONV	195 (20.2%)	244 (25.2%)	0.008
Hypoxemia	8 (0.8%)	8 (0.8%)	> 0.999
Drowsiness	56 (5.8%)	43 (4.4%)	0.180
Dizziness	41 (4.2%)	42 (4.3%)	0.911
Pruritus	14 (1.4%)	23 (2.4%)	0.135
Duration before regaining consciousness (min)	8.0 ± 4.7	7.4 ± 4.3	0.003
Duration before extubation (min)	3.5 ± 2.9	3.2 ± 2.5	0.036

Data are presented as mean ± standard deviation or number (%)
PONV post-operative nausea and vomiting

those in the control group. Pain was the reason most often provided by patients as the cause for their subjective impression of poor sleep, and the provision of pain medications was reported by patients as the most effective means of enabling them to return to sleep [32]. Paradoxically, opioids have been proposed as a cause of postoperative sleep disturbance [33]. Morphine, despite its sedating effect, increases wakefulness and inhibits rapid eye movement (REM) and slow wave sleep (SWS) in a dose-dependent fashion in normal volunteers [34]. These opioids and pain relationship confound postoperative sleep disturbance since pain alone disturbs sleep. Interestingly, this study showed that the reduction in pain intensity in the nalbuphine arm was accompanied by the reduction in opioid consumption as well as improved subjective quality of sleep. While this suggests a possible side benefit of improving sleep quality when using nalbuphine for the control of postoperative pain, it would require a well-designed and controlled study for confirmation. However, in a multicenter, randomized study to assess nalbuphine for pruritus, nalbuphine also reduced sleep latency and disruption. The authors attributed this phenomenon not to a general sedative effect but rather a flow on effect of reducing itch intensity [35].

The adverse effect profile of preemptive nalbuphine from this trial suggested no surprises other than those expected from a centrally acting agonist–antagonist opioid class drug. The time to regaining consciousness and extubation was statistically longer in the nalbuphine group in this study. Sury et al. also reported that addition of nalbuphine to midazolam prolongs the recovery time in fiber optic bronchoscopy patients with improving the quality of sedation [36]. A clinical comparison of buprenorphine, diclofenac, fentanyl, morphine, nalbuphine, pethidine, and placebo in ENT surgery reported that nalbuphine (0.13 $mg{\cdot}kg^{-1}$), given individually as a single i.v. bolus during induction of anesthesia, can provide satisfactory sedation but again with a prolonged recovery time [37]. While the findings that the adverse event rate was not higher in nalbuphine arm compared with placebo, one must be cognizant that the study was conducted in a relative healthy group of patients. A meta-analysis including 15 relatively high-quality randomized trials comparing nalbuphine and morphine reported that the analgesic efficacy of nalbuphine is comparable to morphine, but nalbuphine provides a better safety profile than morphine with respect to certain side effects, especially related to nausea, vomiting, pruritus, and respiratory depression [38]. In the current multicenter study, we also found the incidence of PONV was less with preemptive nalbuphine, and this may be

attributed to its central antagonist activity on the mu receptors [39].

There were certain limitations in this study. First, we did not evaluate the association of the systematic inflammatory response and postoperative pain. Opioid receptors, particularly κ-receptors, are also present on immune cells where they exert an immunomodulatory function and control the release of cytokines [40–42]. In addition, inflammatory cytokines, such as TNF-α, are associated with pain and are involved in the development and maintenance of hyperalgesia [43]. Song et al. demonstrated that TNF-α activation was critical in inflammatory visceral hyperalgesia [44]. Preemptive administration of oxycodone 0.1 $mg{\cdot}kg^{-1}$ in laparoscopic cholecystectomy suppressed the release of TNF-α and alleviated visceral pain postoperatively [45]. These studies suggest that reducing TNF-α production is one of the most effective means of alleviating postoperative visceral pain. A second limitation was the administration of nalbuphine is a single bolus (0.2 $mg{\cdot}kg^{-1}$), and serial doses of nalbuphine need to be studied to determine the optimal dose with the objective as whether nalbuphine could suppress shoulder pain after laparoscopic cholecystectomy. Thirdly, as mentioned above, nalbuphine could improve the quality of sleep after surgery, but we failed to identify the association between the pain intensity, rescue opioid consumption, and nalbuphine. Although this study could be criticized on the basis that it did not use a multimodal analgesic approach that is reflective of contemporary practice [46], the study was designed to specifically evaluate the effect of nalbuphine, and as such necessitated minimizing potential confounding influences. Finally, studies have shown that nalbuphine is a more potent analgesic in women than in men [47], which implies the existence of complex sex-based differences in the circuitry involved in pain modulation and indicates the need for further study.

CONCLUSIONS

In conclusion, this multicenter, randomized controlled trial showed that preemptive nalbuphine administered at a dose of 0.2 $mg{\cdot}kg^{-1}$ was safe and effective at reducing early visceral pain and supplemental analgesic use in patients undergoing laparoscopic cholecystectomy. The study adds to the body of literature that suggests that drugs with pharmacologic actions at κ-opioid receptors might be useful in treating visceral pain conditions including abdominal surgery associated with postoperative pain.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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