Efficacy and safety of flurbiprofen-axetil combined with nalbuphine pretreatment on remifentanil-induced postoperative hyperalgesia: A randomized clinical trial

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Abstract. Remifentanil-induced hyperalgesia (RIH) is a common and complicated issue in patients undergoing laparoscopic cholecystectomy (LC), which significantly reduces patient satisfaction. The present trial was designed to clarify the individual and combined effects of flurbiprofen-axetil and nalbuphine on remifentanil-induced hyperalgesia. This randomized double-blind clinical trial included 120 adult patients who underwent LC at The Second People's Hospital of Wuhu. The individuals were randomized into a flurbiprofen-axetil group (F group), nalbuphine group (N group), flurbiprofen-axetil combined with nalbuphine group (FN group) and saline group (S group). The four groups were given flurbiprofen-axetil (50 mg, iv.), nalbuphine (0.1 mg/kg, iv.), flurbiprofen-axetil (50 mg, iv.) combined with nalbuphine (0.1 mg/kg, iv.) or normal saline respectively prior to skin incision. The primary outcome was the postoperative mechanical pain thresholds at the inner forearm and peri-incisional area. The secondary outcomes were the visual analog scale (VAS) and Ramsay sedation scale at 0.5, 1, 4 and 24 h after surgery, and any other adverse events. The pain threshold of the medial forearm in the FN group did not differ from that in the F and N groups at 24 h after surgery (P=0.310 and P=0.910, respectively). However, the pain threshold around the incision in FN group was significantly lower than that in F and N groups 24 h after surgery (P=0.001). The VAS of the F group, N group and FN group were all significantly lower than that in the S group at 0.5, 1 and 24 h after surgery (P<0.001). No significant differences were observed in the incidence of adverse events between the four groups. Single flurbiprofen-axetil and single nalbuphine effectively prevented RIH 24 h after surgery in LC. The combination of the two analgesic drugs, with different mechanisms of action, was not superior to single therapy. The present study was registered with the Chinese Clinical Trial Registry (registration no. ChiCTR2100045347).

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Introduction

Opioids are widely used during general anesthesia. Among these, remifentanil is an ultra-short-acting μ-opioid receptor agonist (1). Remifentanil has a predictable and rapid recovery that is relatively independent of the dose and duration of infusion; therefore, it can be given in high doses until skin closure is observed with little risk of delayed postoperative recovery or respiratory depression. However, considerable evidence suggests that exposure to high-dose remifentanil paradoxically enhances pain sensitivity and increases analgesic requirements (2,3). A previous cohort study reported that the incidence of postoperative hyperalgesia induced by remifentanil was 41.8% when cumulative intraoperative infusions of remifentanil exceeded 30 μg/kg (4). A corollary of short action is that patients may experience considerable surgical pain and agitation in the immediate postoperative period.

The cyclo-oxygenase (COX) inhibitors flurbiprofen-axetil and nalbuphine have been previously proposed as adjunctive pre-anesthetics and analgesics for postoperative pain control. Nalbuphine is a μ-antagonist and a partial κ-agonist for G-proteins and β-arrestin-2. The role of nalbuphine in the prevention of acute hyperalgesia may be due to its antagonistic effect on μ receptors or modulatory action on central κ-receptors (5). Flurbiprofen-axetil belongs to the propionic acid derivative class of nonsteroidal anti-inflammatory drugs (NSAIDs). Similar to other NSAIDs, flurbiprofen-axetil is a cyclo-oxygenase inhibitor that blocks the formation of prostaglandins, which are implicated extensively in inflammatory lesions and certainly involved with inflammatory pain and connective tissue destruction (6). A previous study reported that spinal COX inhibition may be of importance in preventing acute hyperalgesia following surgery (7). The mechanism of inhibition of hyperalgesia is different in nalbuphine and flurbiprofen-axetil, whether there is a difference between their

preventative and therapeutic effects, and the effect of combined application remains to be elucidated. To provide a reference for clinical medication, the present study compare the effects of nalbuphine and flurbiprofen-axetil alone or in combination on patients with remifentanil-induced hyperalgesia (RIH) during laparoscopic cholecystectomy (LC).

Materials and methods

Study design and participants. A randomized, double-blind, clinical trial was performed at The Second People's Hospital of Wuhu. The trial plan was approved by the Ethics Committee of The Second People's Hospital of Wuhu (approval number: 2021-07) on April 12, 2021. The study was registered with the Chinese Clinical Trial Registry (registration no. ChiCTR2100045347) on April 13th, 2021. Written informed consent was obtained from each patient in the study, which was performed between April 28th, 2021, and January 25th, 2022. The study was performed in accordance with the Declaration of Helsinki.

Patients were 20-65 years old, of any sex, American Society of Anesthesiologists classification I-II, with a body mass index of 18-30 kg/m^2 (8). All patients were scheduled to undergo LC. The exclusion criteria were as follows: i) Allergy or contraindication to the experimental drugs; ii) any serious medical problems other than the diseased gall bladder or psychiatric conditions; iii) pregnancy; iv) a history of alcohol or drug abuse, or chronic use of opioids or sedative drugs; or v) peptic ulcer disease in the active stage. After randomization, if patients required open surgery in the abdomen or if the duration of surgery was >3 h, they were withdrawn from the study.

Randomization and masking. The investigators, who were blinded to the grouping, prepared the randomized schedule. The randomized numbers generated by the computer were enclosed in a sealed envelope. The anesthesiologist received random numbers from the investigators and divided the patients into four groups. The study drugs were packaged in containers with the same color and packaging. Patients were randomly allocated into the flurbiprofen-axetil group (F group), nalbuphine group (N group), flurbiprofen-axetil combined with nalbuphine group (FN group) or saline group (S group) in a 1:1:1:1 ratio. Throughout the study, patients, researchers, anesthesiologists, surgeons, nurses in the post-anesthesia nursing unit and wards, and perioperative observation index recorders were all blinded to the allocation of patients to the study groups.

Study treatments. The day before surgery, the baseline mechanical injury threshold of each patient was assessed. A set of 20 hand-held Von Frey filament (Aesthesio® Precision Tactile Sensory Evaluator, DanMic Global, LLC) were used at 3, 6 and 9 cm distal to the middle of the non-dominant forearm elbow crease to evaluate the threshold of mechanical hyperalgesia and calculate the mean value. Peri incisional mechanical hyperalgesia threshold was measured on an area 2 cm below the incision of the infraumbilical trocar at 3 points (both ends and the middle) and the mean values of hyperalgesia thresholds at these 3 points were calculated and recorded (9). With the patient's eyes closed, the investigator pressed the filament of the Von Frey wire against the skin at a right angle until it bent. The force was applied for 1 sec and then released. The von Frey filament application started at 0.4 g and was increased until the patient felt a pricking sensation. Each measurement was 30 sec apart to avoid potential error caused by temporal summation. On the day of LC, a medical monitor (ULTRAVIEW SL® 2700, Spacelabs Healthcare, Inc.) was used to monitor the pulse, blood pressure, electrocardiogram, oxygenation and end-tidal carbon dioxide. Anesthesia was induced by intravenous administration of remifentanil (1 μg/kg, iv.) and propofol (1-2 mg/kg, iv.). When the bispectral index score (BIS) dropped to between 40-60, rocuronium (0.8 mg/kg, iv.) was administered intravenously in all groups.

Maintenance of anesthesia was performed using 0.3 μg/kg/min remifentanil and 1-3% sevoflurane in all groups. The lowest alveolar concentration was initially set at 2.0% and adjusted gradually to acceptable hemodynamics including the mean arterial blood pressure (MAP; -30 to +15%) and the heart rate (HR; -40 to +15%). Rocuronium (0.2 mg/kg; iv.) was used to maintain muscle relaxation. Ephedrine (10 mg; iv.) was administered when the MAP decreased to <60 mmHg. Atropine (0.5 mg; iv.) was administered when the HR dropped to <45 bpm. Furthermore, granisetron (3 mg; iv.) was administered during the surgery to prevent postoperative nausea and vomiting.

Prior to skin incision, patients receive treatment with placebo (normal saline; 10 ml; iv.) in the S group; flurbiprofen (flurbiprofen axetil; 50 mg; iv.) in the F group; nalbuphine (nalbuphine; 0.1 mg/kg; iv.) in the N group; and flurbiprofen (flurbiprofen axetil; 50 mg; iv.) combined with nalbuphine (nalbuphine; 0.1 mg/kg; iv.) in the FN group. All drugs were diluted to a final volume of 10 ml and the injection time did not exceed 1 min in all groups. The syringe was wrapped in an opaque sticker, and the anesthesiologist and the recorder were blinded to the drug administered.

Following surgery, patients were administered 0.5% ropivacaine solution percutaneously and subcutaneously (a total of 10 ml including 6 ml to the infraumbilical trocar and 4 ml to the other two trocar locations). Following the recovery of adequate spontaneous ventilation and response to verbal commands such as opening of the eyes, the tracheal tube was removed when BIS values reached 80. In terms of postoperative analgesia, the visual analogue scale (VAS, scale 0-10) has been proposed to measure pain intensity: 0 is no pain and 10 is the most severe pain (10). When initial postoperative pain (VAS >4) after surgery was primarily managed using sufentanil (5 μg; iv.) at intervals of 10 min until the VAS score reached <3. After transfer to the general ward, patients were administered two doses of flurbiprofen-axetil (50 mg, ivgtt.) per day. Dezocine (5 mg, iv.) was administered as a rescue analgesic upon patient request or a reported VAS score >4.

Outcomes. The primary outcome was the mechanical hyperalgesia threshold before and 24 h after the operation. The mechanical hyperalgesia threshold was defined as the lowest force (g) necessary to produce a pricking sensation.

The secondary outcomes included VAS and Ramsay sedation scale (RSS) (11) at 0.5, 1, 4, and 24 h after surgery, perioperative hemodynamics (MAP and HR), the number of

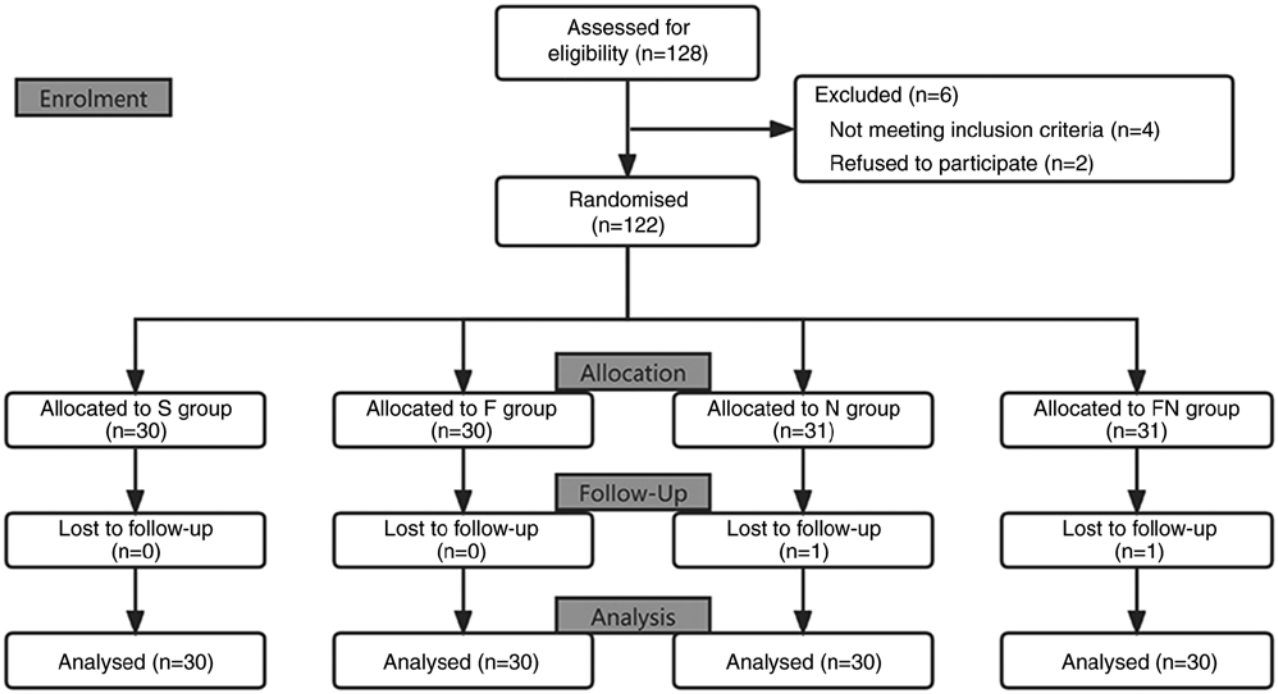

Figure 1. Flow diagram for the present study. Flow diagram of this single-center, double-blind, randomized trial performed on adult patients who underwent LC from April 28, 2021-January 25, 2022. LC, laparoscopic cholecystectomy; S group, 0.3 μg kg^{-1} min^{-1} of remifentanil with saline group; F group, 0.3 μg kg^{-1} min^{-1} of remifentanil with 50 mg of flurbiprofen-axetil group; N group, 0.3 μg kg^{-1} min^{-1} of remifentanil with 0.1 mg kg^{-1} of nalbuphine group; FN group, 0.3 μg kg^{-1} min^{-1} of remifentanil with flurbiprofen-axetil combined with nalbuphine pretreatment.

patients using rescue analgesics at 24 h, and adverse events such as nausea, vomiting, dizziness, headache and hypoxemia. The MAP and HR were continuously measured and were recorded immediately before induction of anesthesia (T1), after induction (T2), after tracheal intubation (T3), after pneumoperitoneum inflation (T4), after gallbladder removal (T5), incision closure (T6) and after tracheal extubation (T7). The six levels of the RSS were used for measurement of the depth of sedation in patients by an experienced anesthesiologist (12).

Statistical analysis. The sample size was calculated based on VAS at 0.5 h after surgery from our preliminary trial. The total sample of 116 subjects achieves 90% power (1-β) to detect differences among the means vs. the alternative of equal means using an F test with a 0.05 significance level (α). The size of the variation in the means is represented by their standard deviation which is 0.42. The common standard deviation within a group is assumed to be 1.16. Considering a possible loss to follow-up, we increased the sample size by 10% (128 subjects for total sample). A Shapiro-Wilk test was used to determine whether the sample population was normally distributed across study parameters ($P<0.05$). Categorical data were presented as the frequency (percentage) and were analyzed using a χ^2 test or Fisher's exact test. Continuous variables were presented as the mean ± SD, or median (interquartile range) and analyzed using a one-way ANOVA or Kruskal-Wallis H test. Mechanical hyperalgesia threshold, VAS, RSS and hemodynamic variables (MAP and HR) were analyzed using a two-way repeated-measures ANOVA for inter-group comparisons. For multiple comparisons, P-values were corrected using Bonferroni's correction. $P<0.05$ was considered to indicate a statistically significant difference. Statistical analysis was performed using SPSS version 25 (IBM Corp.).

Results

Patient characteristics. Between April 28, 2021 and January 25, 2022 a total of 128 patients with LC were enrolled. Of these, 4 patients did not meet the inclusion criteria, 2 patients refused to participate and 2 patients were ruled out as the surgery duration was >3 h. As such, 120 patients were evaluated in the present study: 30 in the F group, 30 in the N group, 30 in the FN group and 30 in the S group (Fig. 1).

No significant differences were observed in the demographics of the four groups. No significant differences were observed in the intraoperative variables in four groups in terms of duration of surgery, duration of anesthesia and medication administered during surgery. There was no significant difference in the pain threshold of the forearm or incision betweeN groups before the operation (Table I). HR and MAP did not significantly differ between the four groups at any of the time points (Fig. 2).

Outcomes. Preoperatively, the mechanical pain threshold on the inner medial forearm was similar in all groups ($P>0.05$). A total of 24 h after the operation, the pain threshold in the S group was significantly lower compared with that prior to the operation. Furthermore, the pain threshold was significantly lower in the S group compared with the F, N and FN groups 24 h after surgery. The pain threshold in the FN group did not differ significantly compared with the F group and N group. There was no significant difference in the pain threshold between the F and N groups (Fig. 3A).

Table I. Patient baseline characteristics and intraoperative variables.

Characteristics and intraoperative variables	S group (n=30)	F group (n=30)	N group (n=30)	FN group (n=30)	P-value
Mean age ± SD, years	45.9±11.7	48.9±12.7	51.2±9.5	47.0±12.3	0.310[a]
Sex, no. (%)					0.825[b]
Female	20 (66.7)	18 (60.0)	21 (70.0)	21 (70.0)	
Male	10 (33.3)	12 (40.0)	9 (30.0)	9 (30.0)	
Mean BMI ± SD, kg/m^2	25.0±2.2	24.8±3.0	25.0±2.4	25.9±2.4	0.355[a]
Median mechanical pain threshold (IQR), g					
Inner forearm	100.0 (60.0, 100.0)	100.0 (60.0, 100.0)	100.0 (60.0, 100.0)	100.0 (60.0, 100.0)	0.579[c]
Surgical incision area	80.0 (60.0, 100.0)	80.0 (60.0, 100.0)	100.0 (60.0, 100.0)	100.0 (60.0, 100.0)	0.742[c]
Median duration of anesthesia (IQR), min	77.0 (67.3, 97.5)	77.5 (63.8, 91.8)	73.5 (65.0, 89.8)	79.0 (65.0, 92.8)	0.697[c]
Median duration of surgery (IQR), min	45.5 (34.8, 65.0)	41.5 (34.8, 65.5)	40.5 (30.0, 54.0)	42.5 (33.5, 65.0)	0.722[c]
Medication administered during surgery					
Median remifentanil (IQR), μg	991.5 (660.8, 1382.8)	837.5 (618.3, 1344.5)	808.5 (605.3, 1044.0)	886.5 (630.0, 1313.3)	0.748[c]
Median rocuronium (IQR), mg	55.0 (45.0, 60.0)	50.0 (45.0, 65.0)	50.0 (45.0, 55.0)	50.0 (50.0, 60.0)	0.540[c]
Median mean sevoflurane (IQR), %	2.8 (2.5, 3.0)	2.8 (2.4, 3.0)	2.9 (2.5, 3.0)	2.8 (2.5, 3.0)	0.427[c]
Median lactated Ringer's solution (IQR), ml	760 (650, 885)	695 (588, 813)	740 (598, 863)	780 (688, 850)	0.407[c]

[a]Analyzed using one-way ANOVA. [b]Analyzed using χ^2 test. [c]Analyzed using Kruskal-Wallis H test. S, 0.3 μg kg^{-1} min^{-1} of remifentanil with saline group; F, 0.3 μg kg^{-1} min^{-1} of remifentanil with 50 mg of flurbiprofen-axetil group; N, 0.3 μg kg^{-1} min^{-1} of remifentanil with 0.1 mg k^{-1}g of nalbuphine group; FN, 0.3 μg kg^{-1} min^{-1} of remifentanil with flurbiprofen-axetil combined with nalbuphine pretreatment; BMI, body mass index; IQR, inter quartile range.

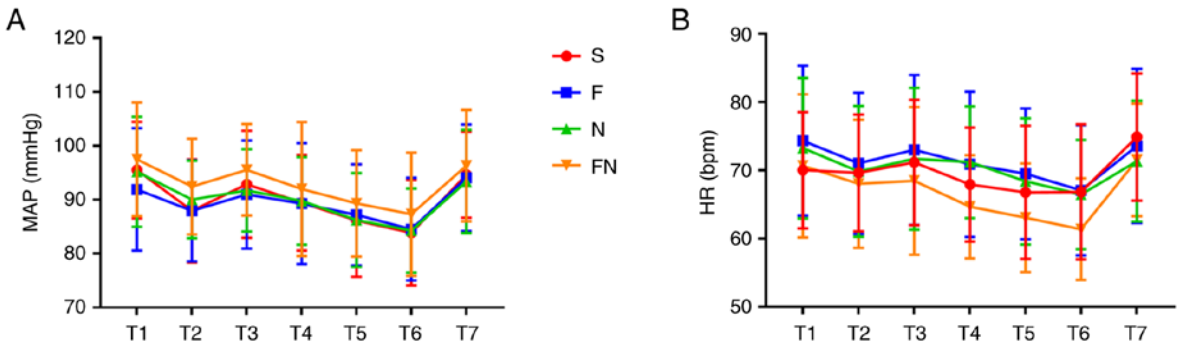

Figure 2. MAP and MAP were assessed during surgery. (A) MAP and (B) HR at different time points during surgery. Data are presented as mean ± standard deviation. MAP, mean arterial pressure; HR, heart rate; S group, 0.3 ug kg^{-1} min^{-1} of remifentanil with saline group; F group, 0.3 ug kg^{-1} min^{-1} of remifentanil with 50 mg of flurbiprofen-axetil group; N group, 0.3 ug kg^{-1} min^{-1} of remifentanil with 0.1 mg kg^{-1} of nalbuphine group; FN group, 0.3 ug kg^{-1} min^{-1} of remifentanil with flurbiprofen-axetil combined with nalbuphine pretreatment; T1, before induction of anesthesia; T2, immediately after induction; T3, immediately after tracheal intubation; T4, immediately after pneumoperitoneum inflation; T5, at gallbladder removal; T6, incision closure; T7, after tracheal extubation.

Preoperatively, the mechanical pain threshold was similar in the peri-incisional area in all groups. The mechanical hyperalgesia thresholds 24 h after surgery were significantly lower in the S group compared with that prior to the operation. Furthermore, the mechanical pain threshold in the S group was significantly lower than that

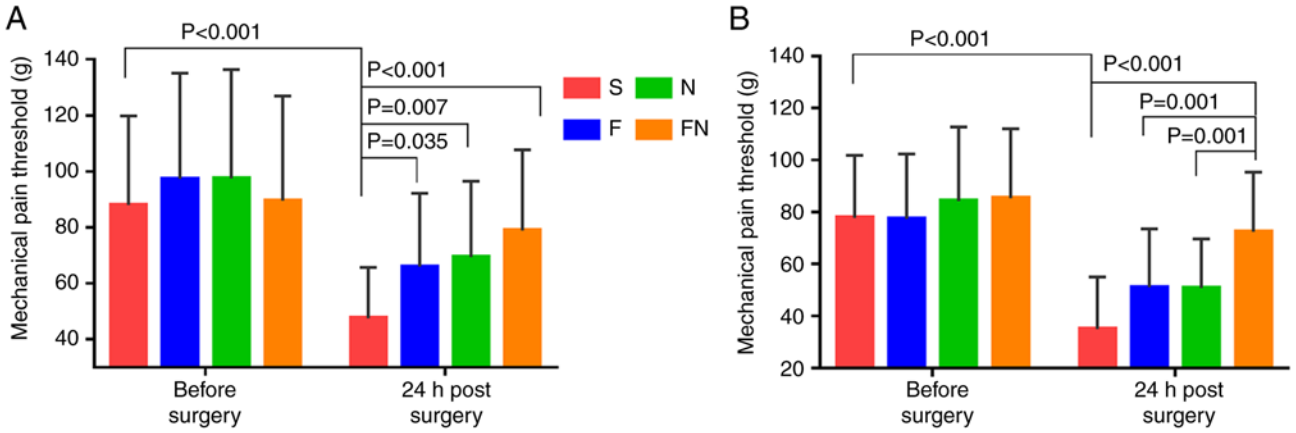

Figure 3. Postoperative mechanical pain thresholds. Pain thresholds were assessed postoperatively at the (A) inner forearm and (B) on the peri-incisional area. The bar charts present mean mechanical pain threshold determined with von Frey wires on the inner forearm and the surgical incision area. S group, 0.3 ug kg^{-1} min^{-1} of remifentanil with saline group; F group, 0.3 ug kg^{-1} min^{-1} of remifentanil with 50 mg of flurbiprofen-axetil group; N group, 0.3 ug kg^{-1} min^{-1} of remifentanil with 0.1 mg kg^{-1} of nalbuphine group; FN group, 0.3 ug kg^{-1} min^{-1} of remifentanil with flurbiprofen-axetil combined with nalbuphine pretreatment.

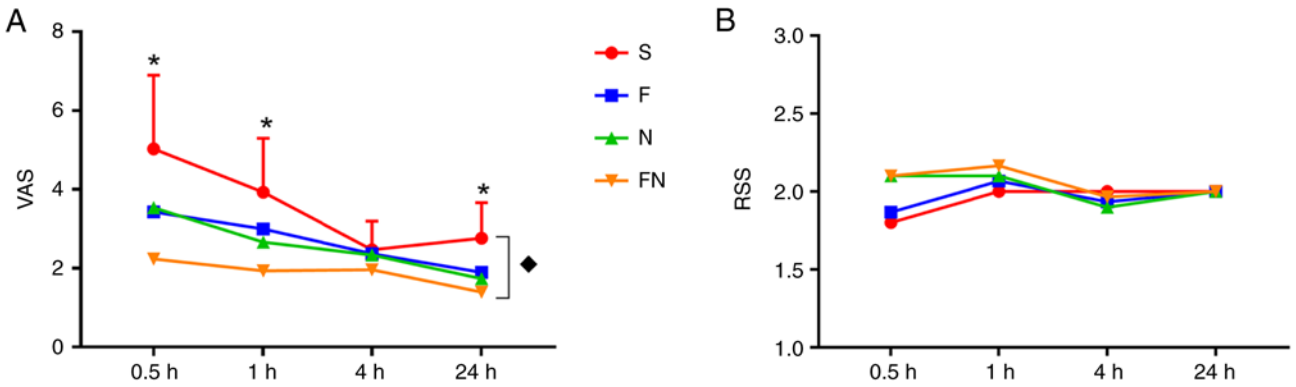

Figure 4. VAS and RSS. (A) VAS and (B) RSS were recorded at 0.5, 1, 4 and 24 h postoperatively. Data are presented as medians (inter-quartile range) or mean ± standard deviation. VAS, visual analog scale; RSS, Ramsay sedation scale; S group, 0.3 ug kg^{-1} min^{-1} of remifentanil with saline group; F group, 0.3 ug kg^{-1} min^{-1} of remifentanil with 50 mg of flurbiprofen-axetil group; N group, 0.3 ug kg^{-1} min^{-1} of remifentanil with 0.1 mg kg^{-1} of nalbuphine group; FN group, 0.3 ug kg^{-1} min^{-1} of remifentanil with flurbiprofen-axetil combined with nalbuphine pretreatment. *P<0.001 vs. F group, N group and FN group. ♦P<0.001 vs. S group.

in the F, N and FN groups 24 h after surgery. There was no significant difference in the pain threshold between the F and N groups. At 24 h post-surgery, the mechanical pain threshold in the FN group was significantly higher than that in the F and N groups (Fig. 3B)

The VAS decreased gradually over time in all groups. At 0.5, 1 and 24 h after surgery, there were statistically significant differences between the S group and the other three groups. There was no significant difference in the VAS between the F and N groups at any of the time points assessed. The VAS of the FN group was significantly lower than that in S groups 0.5, 1 and 24 h after surgery (Fig. 4A). No significant differences were observed in the RSS (Fig. 4B).

There was a statistically significant difference in the number of patients who required sufentanil amongst the four groups. The length of time until sufentanil administration was required in the S group was significantly shorter than that in the other three groups. There was no significant difference in this aspect amongst the F, N and FN groups. The total number of patients taking analgesics within 0.5 h after surgery in the S group was significantly higher than that in the other three groups. There was no significant difference in the postoperative side effects amongst the four groups (Table II).

Discussion

Remifentanil is an ultra-short half-life opioid, that is rapidly metabolized by blood and tissue esterases, works fast, has an excellent analgesic effect and long-term infusion does not result in accumulation in the body, thus reducing the occurrence of delayed awakening (13). However, due to its rapid metabolism and lack of accumulation, its analgesic effects disappear rapidly following withdrawal, inducing opioid-induced hyperalgesia (OIH) and increasing the consumption of analgesic drugs (14,15). Although OIH does not occur as frequently as other adverse reactions associated with opioids, it leads to decreased patient satisfaction. In addition, the incidence of adverse reactions is higher following the addition of opiates, up to 6.2-10.2% (16,17).

The pathogenesis of RIH has been studied previously, with reports including the activation of the central glutamate pathway and the release of excitatory neurotransmitters such

Table II. Postoperative side effects.

Adverse events	S group (n=30)	F group (n=30)	N group (n=30)	FN (n=30)	P-value
Nausea, n (%)	10 (33.3)	4 (13.3)	5 (16.7)	3 (10.0)	0.091[a]
Vomiting, n (%)	5 (16.7)	2 (6.7)	4 (13.3)	3 (10.0)	0.655[a]
Headache, n (%)	1 (3.3)	0	1 (3.3)	1 (3.3)	0.795[a]
Dizziness, n (%)	5 (16.7)	3 (10.0)	3 (10.0)	1 (3.3)	0.397[a]
Respiratory depression, no (%)	0	0	0	0	-
Use of rescue analgesics, n (%)					
0.5 h postoperative period	8 (26.7)	2 (6.7)	3 (10.0)	1 (3.3)	0.045[a]
24 h postoperative period	11 (36.7)	4 (13.3)	5 (16.7)	4 (13.3)	0.069[a]

[a]Analyzed using χ^2 test or Fisher's exact test. S, 0.3 μg kg^{-1} min^{-1} of remifentanil with saline group; F, 0.3 μg kg^{-1} min^{-1} of remifentanil with 50 mg of flurbiprofen-axetil group; N, 0.3 μg kg^{-1} min^{-1} of remifentanil with 0.1 mg kg^{-1} of nalbuphine group; FN, 0.3 μg kg^{-1} min^{-1} of remifentanil with flurbiprofen-axetil combined with nalbuphine pretreatment.

as glutamate and substance P; downregulation of GABA type A receptor (GABAAα_2R) and K^+-cl^-cotransporter-2 (KCC2); activation of dynorphin; activation of n-methyl-d-L-aspartic acid receptor in central sensitization of the posterior horn of the spinal cord; changes in opioid receptor signaling, transient receptor potential channels, increase in cytokines, neurokinin-1 receptors, serotonin antagonist type 3, cholecystokinin and long-term potentiation (LTP) and other transcriptional mechanisms (18-20). Due to the complexity of the mechanism of RIH, it may be necessary to use several drugs with different mechanisms to achieve a suitable effect for the prevention of hyperalgesia. Numerous strategies to alleviate RIH have been previously reported, including the use of minimal doses of remifentanil, gradual withdrawal of remifentanil infusion (21,22), multimodal analgesia, as well as alternative therapy, such as propofol (23), ketamine (24-26), dexmedetomidine (27), N_2O (28) and COX inhibitors (29).

Nalbuphine is a novel synthetic lipophilic opioid receptor agonist, which acts primarily on the κ receptors at the level of the spinal cord and thus acts as a spinal analgesic. It has a long duration of action and can reduce the incidence of adverse reactions (30). Hu *et al* (5) reported that preemptive nalbuphine can reduce postoperative hyperalgesia induced by high-dose remifentanil and could reduce postoperative pain and rescue analgesic consumption in patients undergoing laparoscopic cholecystectomy. Flurbiprofen-axetil is an NSAID, which has anti-inflammatory and analgesic effects via inhibition of prostaglandin synthesis, which reduces the production of inflammatory mediators, and reduces the inflammatory reaction and tissue edema caused by surgical trauma. In a study of healthy volunteers, Lenz *et al* (7) reported that pre-intravenous administration of the COX inhibitor ietorolac inhibited the biosynthesis of prostaglandin E (PGE) by blocking the biological activity of COX, thus inhibiting the activity of N-methyl-D-aspartate (NMDA) receptors, increasing the pain threshold of volunteers, and reducing the central and peripheral pain sensitivity. The present study evaluated whether flurbiprofen-axetil and nalbuphine alone or in combination could prevent RIH and whether the combination was more effective than either treatment alone.

Patients who underwent abdominal surgery have reported more moderate to severe pain in the chest and musculoskeletal sites compared with patients who underwent surgery of the skin and connective tissue (21). A previous study also reported a higher incidence of pain after laparoscopy surgery (31). In a previous review, Yu *et al* (32) reported that an infusion of remifentanil (>0.2 μg/kg/min) was associated with OIH. A study by Schmidt *et al* (33) compared low doses of remifentanil (0.1 μg/kg/min) with high doses (0.4 μg/kg/min) and reported that the mechanical pain threshold decreased more in the high-dose group, and that the low dose of remifentanil (≥0.1 μg/kg/min or ≥12.7 ng/ml) appeared to be sufficient to induce hypersensitivity. The incidence of OIH was reported to be significantly increased at an infusion rate of 0.3±0.2 μg/kg/min, which indicated that high-dose remifentanil was more likely to induce OIH. Therefore, intraoperative remifentanil maintenance was controlled at 0.3 μg/kg/min. Propofol is the most commonly used intravenous anesthetic and there is evidence that propofol may have a modulatory effect on nociceptive processing and perception, and may reduce the hyperalgesia induced by high-dose remifentanil during intravenous anesthesia (23,34), which may improve postoperative outcomes and analgesic drug consumption. Therefore, in the present study, inhalation of volatile agents was used to maintain anesthesia (to reduce the interference of propofol in the results of the experiment) with the concentration adjusted according to BIS value and vital signs during surgery. The circulation of patients in all four groups was stable during surgery.

The effect of RIH appeared to be greatest in the early postoperative period (32). Postoperative pain usually occurs between 24 and 72 h after surgery (35,36). Most patients who undergo laparoscopic cholecystectomy are discharged on the day of surgery or the second day after surgery (37). It is more difficult to evaluate and collect data for such patients at 48 h and beyond post-surgery. Hu *et al* (5) reported that the pain threshold of remifentanil induced postoperative hyperalgesia in the control group was significantly lower than the preoperative baseline 24 h after surgery, but there was no significant difference 48 h after surgery. Therefore, the appropriate indicators measured for 24 h after surgery was used to determine

whether there was an abnormal decrease in pain threshold following opioid administration, characterized by increased perception of pain following opioid-based anesthesia and surgery. The primary measured outcome of the present study was the use of von Frey filaments to assess the mechanical pain threshold. As pain is a subjective and complex proprioceptive sensation, the mechanical pain field was produced by the stimulation of a δ fiber in the skin, which is safe, reliable and easy to use method. In addition, given the complexity of the clinical situation, the pain threshold was measured and the VAS was recorded at each time point after surgery to better evaluate the effect of analgesia.

At 24 h post-surgery, the forearm and incision pain thresholds in all four groups were markedly lower than those prior to surgery, which indicated that continuous infusion of high-dose remifentanil could induce marked hyperalgesia, this was in line with a study by Angst *et al* (38) on the effect of remifentanil on hyperalgesia in volunteers. There were significant differences in the pain threshold in the forearm and incision among the four groups. After surgery, the pain threshold of the forearm and incision was significantly higher in the F group compared with that in the S group, which was consistent with the results of a study by Zhang *et al* (39). The mechanism may be related to the inhibition of TNF-α and 5-HT release, the alleviation of pain caused by Kinin and cytokines, and the interaction with endogenous opioid peptides. However, the mechanism could also be related to the inhibitory effect of COX-2 inhibitors on the activity of central NMDA receptors. Shimoyama *et al* (40) reported the role of NMDA receptors in the development of opioid tolerance and hyperalgesia in a rat model by administering 18-polyphosphate antisense oligodeoxynucleotides to interrupt the upregulation of NMDA receptors. As to the mechanism of COX inhibitors acting on RIH, it has been reported that COX inhibitors antagonize the activation of NMDA receptors and COX inhibition in the spinal cord serves an important role in decreasing hypersensitivity (7). This may be the reason why COX inhibitors serve an important role in the prevention of postoperative acute hyperalgesia. The pain threshold 24 h after surgery in the N group was significantly higher than that in the S group, consistent with the findings of Hu *et al* (5). The specific mechanism of nalbuphine to prevent RIH is not clear; however, it may be related to its activation of κ-receptors and its promotion of spinal analgesia (30). The brain and spinal cord are the primary sites of κ-receptors and the activation of κ-receptors has a strong analgesic effect; therefore, nalbuphine may promote the reduction of postoperative hyperalgesia. Another possibility is that the activation of opioid receptors in the dorsal root of the spinal nerve promotes the release of excitatory neuropeptides. Blocking these opioid receptors in advance could achieve the goal of preemptive analgesia (41). One of the mechanisms of RIH is the release of Dynorphin, Dynorphin is a κ-opioid receptor-specific ligand with endogenous anti-opioid effects (42). However, nalbuphine is also a κ-opioid receptor agonist; therefore, it was hypothesized that nalbuphine competes with Dynorphin for the κ-opioid receptor and has an inhibitory effect on hyperalgesia; however, this needs to be further assessed in future studies.

The forearm and incision pain thresholds 24 h after surgery in the FN group were significantly higher than those in the S group, which supported the aforementioned hypothesis that Flurbiprofen-axetil combined with nalbuphine can prevented RIH effectively. The pain threshold in the incision of the FN group was significantly higher than that in the F and N groups; however, the pain threshold in the forearm of the FN group did not differ significantly from those of the F and N groups. The pain threshold can be induced either by drugs, such as remifentanil, or as a surgical nociceptor, a consequence of tissue and nerve trauma (43). Therefore, incision pain threshold may be a better indicator of RIH in patients with trauma.

Shortly after the cessation of remifentanil infusion, the pain grades in the F group, N group, and FN group were all markedly lower than those in the control group. The analgesic effect was greatest 30 min after cessation of infusion, and the analgesic demand in the S group was significantly higher than that in the other three groups 30 min after surgery, although there was no significant difference in the total demand among the four groups, which indicated that patients in the S group experienced moderate and severe pain relatively sooner after surgery compared with the other drugs. At 0.5 h after surgery, 8 patients (26.7%) in S group used rescue analgesics within the PACU, which was more than that in the other three groups, but the total number of patients requiring rescue analgesics within 24 h did not differ significantly among the four groups.. The VAS gradually decreased over time in all groups, but compared with the other three groups, the S group still maintained a markedly higher VAS at 0.5, 1 and 24 h after surgery. At 4 h after surgery, there was no significant different between the four groups. This may be related to the gradual improvement of the inflammatory response or the gradual activation of NMDA receptors by postoperative flurbiprofen-axetil.

Previous studies have reported a poor association between opioid-induced hyperalgesia and postoperative pain (44,45). However, a correlation between pain intensity or relief analgesic consumption and pain threshold was demonstrated in the present study. This may be due to a multifactorial modulation of clinical pain. In addition, there was no significant difference in adverse events between the four groups, which may be related to the high dose of remifentanil activating the μ-opioid receptor (46), and the need for postoperative analgesic drugs, such as sufentanil and dezocine. Nalbuphine can reduce the incidence of opioid-associated adverse reactions such as nausea, vomiting and skin pruritus related to G-protein interactions (47). Nalbuphine can even reverse the opioid-induced respiratory depression (42). However, in the present study, the incidence of nausea and vomiting in the N group was not significantly lower than that in the S group. This may be due to the small sample size in the present study and further expansion of the sample size is needed properly assess the effects of nalbuphine in this respect. Adverse events associated with NSAID were generally rare, with occasional alimentary tract adverse reactions (48).

The present study has several limitations. Firstly, the present study was a single-center study, and only one surgical method was used as the research background, which may have resulted in a selection bias. Secondly, hyperalgesia was measured using a specific instrument (von Frey filament) and there may be errors in this manual measurement. The

analgesic flurbiprofen-axetil was routinely administered postoperatively, and if the VAS was >4, 10 mg dezocine was administered intramuscularly, the administration of these drugs may be a confounding factor in the results of the present study; however, the findings of the present study may apply to real world clinical settings. The criteria for intraoperative drug administration require further study to compare the differences between single or multiple-dose regimens, or alternate continuous-infusion regimens. Finally, the present study, only followed patients for 24 h after surgery, and did not show any effect of preemptive analgesia on chronic pain due to hyperalgesia; therefore, further studies are required to evaluate these clinical results to guide the management of chronic pain, given that the management of chronic postoperative pain remains a challenge for anesthesiologists and surgeons.

In conclusion, both flurbiprofen-axetil alone and nalbuphine alone effectively prevented RIH 24 h after surgery in LC. The combination of two analgesic drugs with different mechanisms of action was not superior to monotherapy.

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Availability of data and materials

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

Author contributions

YZ and HM designed the study and wrote the first draft of the manuscript. YZ, HM and JZ collected the clinical data. YL designed the study and revised the manuscript. YZ and HM confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the ethics committee of The Second People's Hospital of Wuhu (approval number: 2021-07) on April 12, 2021. Written informed consent was obtained from each patient.

Patient consent for publication

Written informed consent for publication was obtained from all the patients.

Competing interests

The authors declare that they have no competing interests.

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