

Preemptive Nalbuphine Attenuates Remifentanyl-Induced Postoperative Hyperalgesia After Laparoscopic Cholecystectomy: A Prospective Randomized Double-Blind Clinical Trial

This article was published in the following Dove Press journal:
Journal of Pain Research

Jun Hu^{1,2}
Shuangshuang Chen³
Mudan Zhu³
Yun Wu^{1,2}
Ping Wang³
Jinbao Chen³
Ye Zhang^{1,2}

¹Department of Anesthesiology, The Second Hospital of Anhui Medical University, Hefei, People's Republic of China; ²Key Laboratory of Anesthesiology and Perioperative Medicine of Anhui Higher Education Institutes, Anhui Medical University, Hefei, Anhui, People's Republic of China; ³Department of Anesthesiology, Tongling People's Hospital of Anhui Medical University, Tongling, Anhui, People's Republic of China

Background: Remifentanyl-induced hyperalgesia (RIH) is a paradoxical phenomenon that may increase sensitivity to painful stimuli. Nalbuphine, which is both a μ -receptor antagonist and κ -receptor agonist, may affect RIH. The aim of this study was to evaluate the effects of nalbuphine on RIH during laparoscopic cholecystectomy.

Methods: A total of 96 patients were divided into the following four groups: 0.4 $\mu\text{g}/\text{kg}/\text{min}$ of remifentanyl with 0.2 mg/kg of nalbuphine (HRNA), 0.4 $\mu\text{g}/\text{kg}/\text{min}$ of remifentanyl with saline (HRSA), 0.1 $\mu\text{g}/\text{kg}/\text{min}$ of remifentanyl with 0.2 mg/kg of nalbuphine (LRNA), and 0.1 $\mu\text{g}/\text{kg}/\text{min}$ of remifentanyl with saline (LRSA). The pain thresholds of postoperative mechanical hyperalgesia were measured with von Frey filaments. Pain intensity and analgesic consumption were recorded up to 48 h after surgery.

Results: Pain thresholds on the inner forearm decreased in the HRSA group compared with the HRNA ($P = 0.0167$), LRNA ($P = 0.0027$), and LRSA ($P = 0.0318$) groups at 24 h after surgery. Pain thresholds on the peri-incisional area decreased in the HRSA group compared with HRNA, LRNA, and LRSA (all $P < 0.0001$) groups at 24 h after surgery. Patients in the HRNA group showed lower numeric rating scale scores at 1 h ($P = 0.0159$), 3 h ($P = 0.0118$), 6 h ($P = 0.0213$), and 12 h ($P = 0.0118$) than those in the HRSA group. Postoperative requirement for sufentanil was greater in the HRSA group than the HRNA group during the first 3 h ($P = 0.0321$) and second 3 h ($P = 0.0040$). Postoperative sufentanil consumption was also greater in the LRSA group than in the LRNA group during the first 3 h ($P = 0.0321$) and second 3 h ($P = 0.0416$).

Conclusion: Preemptive nalbuphine can ameliorate postoperative hyperalgesia induced by high-dose remifentanyl in patients undergoing laparoscopic cholecystectomy.

Keywords: hyperalgesia, nalbuphine, remifentanyl, pain threshold

Introduction

Laparoscopic cholecystectomy is one of the most commonly performed surgical procedures in the world. Fast-track anesthesia has been proposed as the best choice for this short procedure as it offers enhanced recovery after surgery and decreased loss of functional capacity.¹ Anesthesia with remifentanyl is considered an effective fast-track anesthesia with both rapid induction and emergence for short surgeries.²

Correspondence: Ye Zhang
Department of Anesthesiology, The Second Hospital of Anhui Medical University, 678 Furong Road, Hefei 230601, People's Republic of China, Tel +86-551-63869625
Email zhangye_hassan@sina.com

However, remifentanyl is a potent μ opioid receptor agonist with rapid onset and offset and has been consistently associated with the development of remifentanyl-induced hyperalgesia (RIH), a paradoxical phenomenon whereby a patient receiving opioids for intraoperative pain control may have increased postoperative sensitivity to painful stimuli.³ Postoperative hyperalgesia usually results in unsatisfactory pain control, and increased postoperative pain has become the most common reason for prolonged convalescence after laparoscopic cholecystectomy.^{4,5}

The underlying mechanisms of RIH are likely associated with alteration of N-methyl-D-aspartate (NMDA) receptor or μ -receptor activities. Research has shown that administering an opioid receptor antagonist such as naloxone before remifentanyl infusion may attenuate hyperalgesia development but does not reduce postoperative pain.⁶ Nalbuphine is a semisynthetic opioid analgesic with mixed μ -receptor antagonist and κ -receptor agonist characteristics and a weak affinity to δ -receptors.⁷ It is as potent as morphine for providing analgesia but without the propensity for respiratory depression and drug addiction.⁸ In preclinical models of capsaicin-induced thermal hypersensitivity, nalbuphine produced a dose-dependent antiallodynic effect;⁹ however, whether its preemptive administration could provide more satisfactory pain control and modulate postoperative RIH after laparoscopic cholecystectomy remains unknown.

To address this question, we investigated the antihyperalgesic and analgesic effects of preemptive nalbuphine administration before anesthesia in patients undergoing laparoscopic cholecystectomy. We believe our results provide useful information that could guide the future use of nalbuphine under remifentanyl-based fast-track anesthesia for short surgeries.

Materials and Methods

Patients

This single-center, prospective, randomized, parallel-group, double-blind study was conducted between January and June 2019. The study was performed in compliance with the Declaration of Helsinki and registered in the Chinese Clinical Trial Registry (ChiCTR1800020209). It was approved by the Ethics Committee of the Tongling People's Hospital of Anhui University, and written informed consent was obtained from the patients before surgery. Patients with an American Society of Anesthesiologists physical status of I–II, aged 18–60 years, and undergoing elective laparoscopic cholecystectomy under general anesthesia were included.

The exclusion criteria were as follows: bronchial asthma; severe hypertension; coronary heart disease; diabetes mellitus; obesity (body mass index [BMI]>30 kg/m²); cardiac, hepatic, or renal dysfunction; psychiatric disease; history of chronic pain; history of alcohol or opioid abuse; chronic use of opioids; intake of any analgesic within 48 h before surgery; pregnancy; allergy or contraindication to nalbuphine; or incapacity to comprehend pain assessment instructions. After randomization and allocation, patients were withdrawn from the study if laparoscopy was converted to open surgery or if they required reoperation for any reason.

Randomization and Masking

Subjects were randomly assigned to one of the four groups in a 1:1:1:1 ratio. A random sequence was generated using a computer-generated randomization program and kept in sealed envelopes by an assistant not involved in the trial. On the morning of the surgery, the assistant opened a sealed envelope and prepared the drugs in identical syringes according to the group allocation. The anesthesiologist who administered the injections, the outcome assessor, and the subjects were blinded to the allocation and study drugs. All investigators and patients were blinded to the group assignment.

Anesthesia and Drug Intervention

Nurses not involved in the study prepared remifentanyl, nalbuphine, and normal saline according to the group assignment. Two investigators performed anesthetic management according to a predetermined protocol. Patients were monitored with non-invasive blood pressure, pulse oximetry, electrocardiography, and bispectral index (VISTA™ monitoring system; Aspect Medical Systems Inc., Norwood, MA, USA). Patients were randomly assigned to one of four groups depending on the intraoperative infusion concentration of remifentanyl with or without a preemptive administration of nalbuphine before anesthesia: 0.4 μ g/kg/min of remifentanyl with 0.2 mg/kg of nalbuphine (HRNA), 0.4 μ g/kg/min of remifentanyl with saline (HRSA), 0.1 μ g/kg/min of remifentanyl with 0.2 mg/kg of nalbuphine (LRNA), and 0.1 μ g/kg/min of remifentanyl with saline (LRSA). Nalbuphine and saline were administered during a 10-min period before anesthetic induction. General anesthesia was induced by intravenous (i.v.) midazolam (0.05 mg/kg), propofol (0.8–1.2 mg/kg), rocuronium (0.6 mg/kg), and bolus remifentanyl (1.5 μ g/kg). After the onset of muscle relaxation, the patients were intubated with a video laryngoscope. An endotracheal tube was inserted with inner diameters of 7.0 and 7.5 mm for

women and men, respectively. Mechanical ventilation was performed in volume-controlled ventilation mode to achieve an adjusted end-tidal carbon dioxide content of 35–45 mmHg with variables and an inspired oxygen fraction of 0.5 with a fresh gas flow 2 L/min of oxygen and air. Anesthetic depth was maintained at a bispectral index of 40–60 by adjusting the end-tidal sevoflurane concentration. Muscle relaxation was maintained with intermittent doses of rocuronium. Intravascular volume treatment was controlled in all groups with lactated Ringer's solution to maintain a stable fluid balance. Bradycardia (heart rate [HR] <40 beats/min) was treated with i.v. atropine 0.5 mg. Hypotension, defined as mean arterial blood pressure (MAP) <60 mm Hg for 1 min, was treated with i.v. ephedrine 5 mg or phenylephrine 30 µg as appropriate. At skin closure, administration of sevoflurane and remifentanyl was discontinued. After procedure completion, muscle relaxation was reversed as appropriate, and the endotracheal tube was removed. After confirming adequate spontaneous breathing, responses to verbal commands, and opening their eyes, the patient was transferred to the postanesthesia care unit (PACU).

Outcomes and Measurements

The investigator assessed pain thresholds to mechanical stimuli threshold using 20 hand-held Von Frey filaments (North Coast Medical Inc., Gilroy, CA, USA) in an area 2 cm around the incision and on the dominant inner forearm at 3-, 6-, and 9-cm distal to the antecubital crease according to the published methods.^{6,10–12} Every position was measured three times at 15-s intervals, and a mean value was calculated for statistical analysis. The mechanical hyperalgesia threshold was defined as the smallest force (in grams) necessary to bend a Von Frey filament that was detected as painful by the patient. The test was performed preoperatively and 24 and 48 h after surgery.

An investigator evaluated pain intensity using an 11-point numeric rating scale (NRS): 0 = no pain; 10 = worst imaginable pain at six time points: 1, 3, 6, 12, 24, and 48 h after surgery. Patients with an initial pain score >4 received i.v. sufentanil, which was administered in 5-µg doses at 30-min intervals until NRS <3. Rescue analgesic medication quantities were recorded.

MAP and HR were continuously measured and recorded before administration of nalbuphine or saline at baseline (T1), 10 min later after intervention was initiated but before induction (T2), immediately after induction (T3), immediately after tracheal intubation (T4), immediately after pneumoperitoneum inflation (T5), incision

closure (T6), and tracheal extubation (T7). The amounts of anesthetic drugs and fluid requirements during surgery and the lengths of stay in the PACU and hospital were recorded.

The primary outcomes were the postoperative pain thresholds on the peri-incisional area and the dominant inner forearm. The secondary outcomes were postoperative rescue analgesic requirement, pain intensity, intraoperative hemodynamic variables, and amounts of drugs or fluid.

Statistical Analysis

The pain threshold of the dominant inner forearm was the primary outcome. In the literature, the mean mechanical hyperalgesia threshold of the dominant forearm at baseline was 95.5 g.^{10,11} We estimated a difference of at 25% (error standard deviation = 25.0) among the intervention groups. A sample size of 22 patients per group was found to be sufficient to detect a significant difference ($\alpha = 5\%$) with a statistical power (β -value) of 0.8, and we increased the sample size by 15% to reach 24 patients per group to allow dropouts.

Continuous variables are presented as mean (standard deviation) or median (interquartile range) depending on normality as assessed with the Shapiro–Wilk test. Homogeneity of variance was checked by the Levene test. Mechanical hyperalgesia threshold, NRS scores and hemodynamics were analyzed by two-way repeated measure analysis of variance (ANOVA) with Bonferroni post hoc comparisons. Data such as age, BMI, mean concentration of sevoflurane, durations of surgery and anesthesia, and length of PACU and hospital stays were also analyzed using one-way ANOVA, Kruskal–Wallis test, unpaired or paired *t*-tests, and Mann–Whitney U or Wilcoxon signed-rank tests as appropriate. Categorical variables were compared with χ^2 tests. All analyses were conducted in an intention-to-treat manner. $P < 0.05$ was considered statistically significant. SPSS 20.0 software (IBM Corporation, Armonk, NY, USA) was used for all statistical analyses.

Results

From January to June 2019, 100 Laparoscopic cholecystectomy patients were screened for inclusion; 2 met exclusion criteria, and 2 refused to participate. Ultimately, 96 eligible subjects were included and randomized to 4 equal groups of 24 (Figure 1). The four groups were comparable with respect to demographic characteristics and showed no differences in pre- and intraoperative factors including

mean end-tidal concentrations of sevoflurane, propofol, and rocuronium doses, and operative time (Table 1).

Primary Outcome: Mechanical Hyperalgesia Threshold

As shown in Figure 2A, the baseline mechanical pain thresholds on the inner forearm were similar among all groups ($P > 0.05$). Pain thresholds were significantly lower in the HRSA group at 24 h after surgery than the pre-operative baseline ($P < 0.0001$). Furthermore, they were decreased in the HRSA group compared with the HRNA ($P = 0.0167$), LRNA ($P = 0.0027$), and LRSA ($P = 0.0318$) groups at 24 h. However, no significant difference was detected at 48 h after surgery. Baseline mechanical pain thresholds on the peri-incisional area were comparable in all groups ($P > 0.05$, Figure 2B). Compared with baseline, pain thresholds were decreased in the HRSA group at 24 and 48 h after surgery (both $P < 0.0001$). Furthermore, pain thresholds were decreased in the HRSA group compared with the HRNA, LRNA, and LRSA groups 24 h after surgery (all $P < 0.0001$). At 48 h after surgery, pain thresholds in the HRSA group were significantly lower than in the LRNA and LRSA groups (both $P < 0.0001$). The pain threshold in the HRNA group was lower 48 h after surgery than at baseline ($P = 0.0018$). At 48 h after surgery, pain thresholds were

lower in the HRSA group than the LRNA and LRSA groups (both $P < 0.0001$), and the pain threshold in the HRNA group was significantly lower than in the LRNA ($P = 0.0017$) and LRSA ($P = 0.0062$) groups.

Postoperative Pain Intensity and Sufentanil Consumption

NRS scores all gradually decreased over time in all groups (Figure 3). Patients in the HRNA group reported lower NRS scores at 1 h ($P = 0.0159$), 3 h ($P = 0.0118$), 6 h ($P = 0.0213$), and 12 h ($P = 0.0118$) than those in the HRSA group. Patients in the LRNA group had lower NRS scores at 3 h ($P = 0.0118$) and 6 h ($P = 0.0213$) than those in the LRSA group. The numbers of patients who received postoperative sufentanil were significantly different among the four groups ($P = 0.0308$) (Table 2). Sufentanil consumption was greater in the HRSA group than the HRNA group during the first 3 h ($P = 0.0321$) and second 3 h ($P = 0.0040$). Postoperative sufentanil consumption was also greater in the LRSA group than the LRNA group during the first 3 h ($P = 0.0321$) and second 3 h ($P = 0.0416$) (Table 3).

Hemodynamic Parameters

As shown in Figure 4A, HR was higher in the LRSA group at T4 ($P = 0.0438$), T5 ($P = 0.0039$), and T6 ($P = 0.0049$) than in the HRSA group. The LRNA group's HR was also

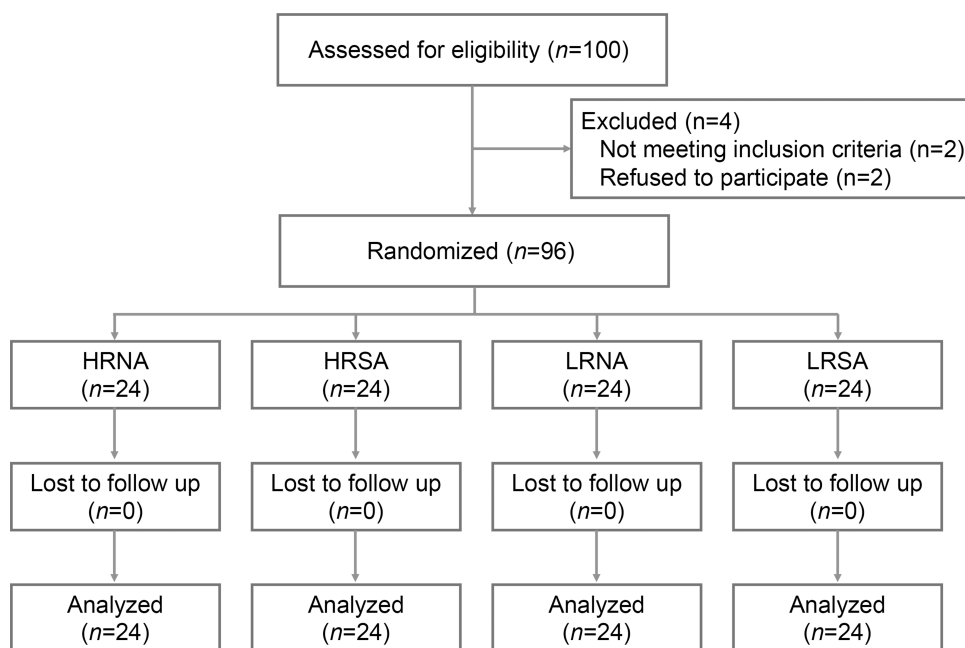


Figure 1 CONSORT flow diagram. HRNA, 0.4 $\mu\text{g}/\text{kg}/\text{min}$ of remifentanyl with 0.2 mg/kg of nalbuphine group; HRSA, 0.4 $\mu\text{g}/\text{kg}/\text{min}$ of remifentanyl with saline group; LRNA, 0.1 $\mu\text{g}/\text{kg}/\text{min}$ of remifentanyl with 0.2 mg/kg of nalbuphine group; LRSA, 0.1 $\mu\text{g}/\text{kg}/\text{min}$ of remifentanyl with saline group.

Table 1 Patient Demographics

Characteristic	HRNA	HRSA	LRNA	LRSA	P value
Age (years)	52 (45–57)	54 (39–55)	49 (42–53)	53 (48–61)	0.2875
Sex (male/female)	5/19	6/18	6/18	8/16	0.7946
BMI (kg/m ²)	23.3 (2.6)	22.4 (2.4)	22.8 (2.5)	22.5 (2.2)	0.5587
ASA grade					
I (n)	11	13	15	12	0.6906
II (n)	13	11	9	12	
Hypertension (n)	4	3	2	5	0.6047
Diabetes mellitus (n)	3	2	3	1	0.7177
Amount of anesthetic drugs					
Propofol (mg)	48 (7)	46 (8)	47 (10)	48 (7)	0.5046
Mean sevoflurane concentration (%)	2.8 (0.3)	2.8 (0.3)	2.9 (0.3)	2.8 (0.3)	0.4550
Remifentanyl (mg)	1.8 (4.9)	1.7 (4.4)	0.4 (1.3)	0.4 (0.9)	0.0001
Rocuronium (mg)	59 (20)	55 (17)	57 (17)	59 (14)	0.8859
Lactated Ringer's solution (mL)	763 (145)	698 (166)	743 (131)	785 (129)	0.1921
Duration of surgery (min)	54 (20)	51 (15)	53 (15)	52 (13)	0.9517
Duration of anesthesia (min)	66 (20)	60 (15)	61 (20)	65 (17)	0.6094

Notes: Data are presented as mean (standard deviation) except age median (interquartile range) or number of patients. ASA, American Society of Anesthesiologists; BMI, body mass index; HRNA, 0.4 µg/kg/min of remifentanyl with 0.2 mg/kg of nalbuphine group; HRSA, 0.4 µg/kg/min of remifentanyl with saline group; LRNA, 0.1 µg/kg/min of remifentanyl with 0.2 mg/kg of nalbuphine group; LRSA, 0.1 µg/kg/min of remifentanyl with saline group.

higher than that of the HRSA group at T4 ($P = 0.0104$) and T5 ($P = 0.0003$). However, there were no differences in HRNA vs HRSA or LRNA vs LRSA. MAP was higher in the LRSA group at T4 ($P < 0.0001$) and T5 ($P = 0.0004$) than in the HRSA group (Figure 4B). The MAPs were also higher in the LRNA group at T4 ($P = 0.0001$) and T5 ($P = 0.0046$) than in the HRSA group. There were no differences for HRNA vs HRSA and LRNA vs LRSA during all time points.

There were no significant differences in the lengths of stay in the PACU or hospital (Table 2). No postoperative adverse events or complications were observed in any group (Table 4).

Discussion

This prospectively randomized clinical trial confirmed that intraoperative administration of high-dose remifentanyl (0.4 µg/kg/min) compared with low-dose remifentanyl

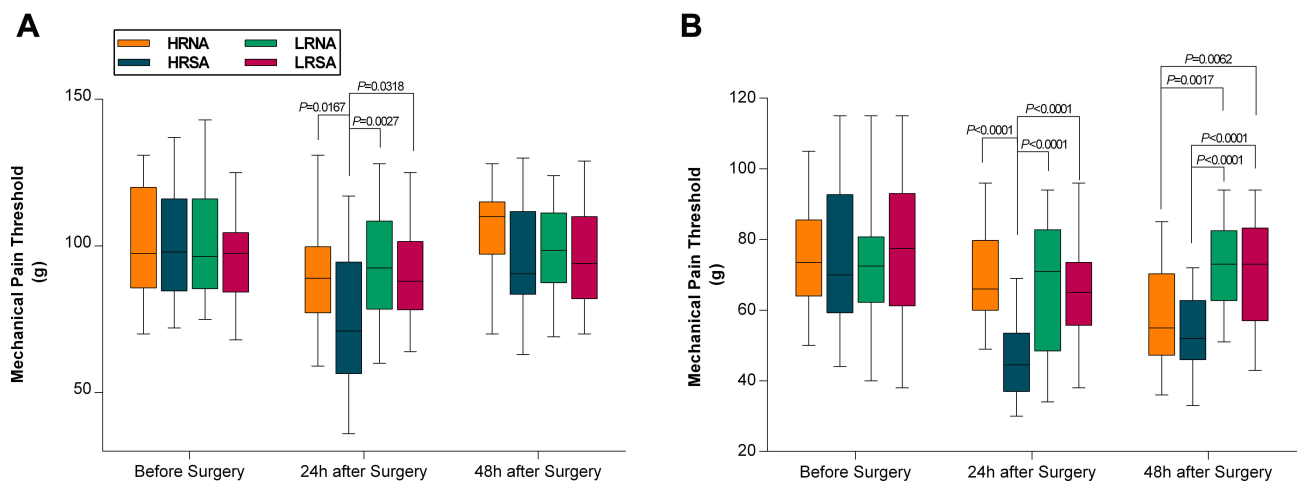


Figure 2 Postoperative mechanical pain thresholds at the inner forearm (A) and on the peri-incisional area (B). The boxes show means and 25–75th percentiles, whiskers indicate the minimum and maximum. HRNA, 0.4 µg/kg/min of remifentanyl with 0.2 mg/kg of nalbuphine group; HRSA, 0.4 µg/kg/min of remifentanyl with saline group; LRNA, 0.1 µg/kg/min of remifentanyl with 0.2 mg/kg of nalbuphine group; LRSA, 0.1 µg/kg/min of remifentanyl with saline group.

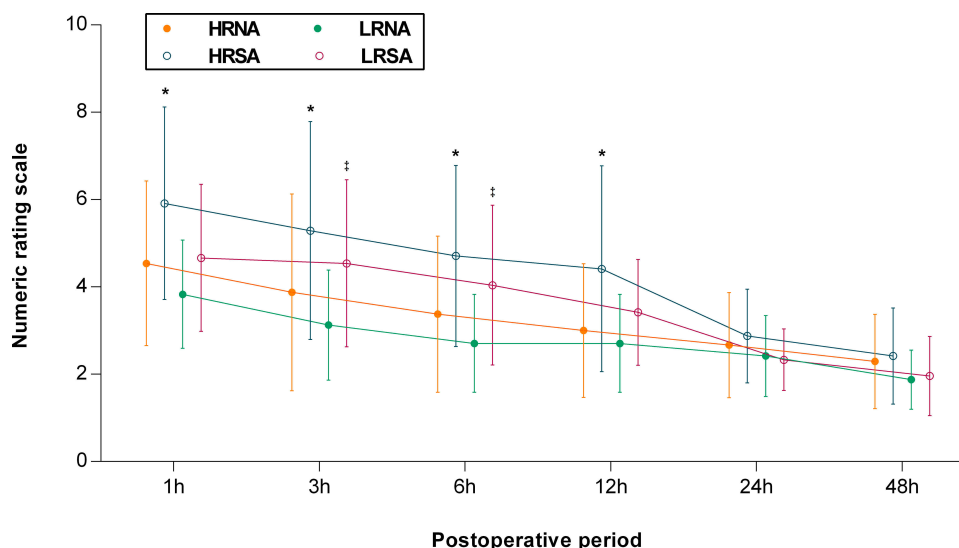


Figure 3 Postoperative pain intensity assessed on an 11-point numeric rating scale (0, no pain; 10, worst pain imaginable). Data are presented as mean (standard deviation). HRNA, 0.4 $\mu\text{g}/\text{kg}/\text{min}$ of remifentanyl with 0.2 mg/kg of nalbuphine group; HRSA, 0.4 $\mu\text{g}/\text{kg}/\text{min}$ of remifentanyl with saline group; LRNA, 0.1 $\mu\text{g}/\text{kg}/\text{min}$ of remifentanyl with 0.2 mg/kg of nalbuphine group; LRSA, 0.1 $\mu\text{g}/\text{kg}/\text{min}$ of remifentanyl with saline group. * $P < 0.05$ vs HRNA, ‡ $P < 0.05$ vs LRNA.

(0.1 $\mu\text{g}/\text{kg}/\text{min}$) increased the incidence of postoperative hyperalgesia, pain scores, and sufentanil requirements after surgery, in agreement with previous studies.^{3,6} We found that preemptive nalbuphine reduced the incidence of postoperative hyperalgesia and decreased pain scores in the high-dose remifentanyl group compared with using high-dose remifentanyl alone. Furthermore, adding nalbuphine to remifentanyl-based anesthesia significantly reduced postoperative sufentanil consumption with effective pain control in patients undergoing laparoscopic cholecystectomy. Intraoperative high-dose remifentanyl seems to effectively dampen intraoperative noxious stimuli by attenuating increases in the HR and MAP induced by tracheal intubation and pneumoperitoneum inflation compared with the low-dose, but caution should be taken to avoid inducing RIH.

RIH is defined as a state of nociceptive sensitization that is characterized by lower mechanical/pressure/cold/pain thresholds following remifentanyl use. To test the effect of nalbuphine on postoperative RIH, remifentanyl infusion was

performed at a constant rate of 0.1 or 0.4 $\mu\text{g}/\text{kg}/\text{min}$, and anesthesia depth was maintained with sevoflurane. It has been reported that sevoflurane does not affect pro-nociceptive thresholds.¹³ Infusion of remifentanyl at 0.4 $\mu\text{g}/\text{kg}/\text{min}$ is widely considered to cause RIH.^{14,15} To more accurately evaluate RIH, no other intraoperative opioids were administered. As expected, compared with low-dose remifentanyl exposure, high-dose remifentanyl infusion decreased the nociceptive thresholds both on the forearm and peri-incisional area. In line with our result, remifentanyl also decreased the pain thresholds in the forearm and around the incision 24 h after laparoscopic gynecological surgery.¹⁰ Unfortunately, Koo et al⁶ reported that postoperative pain thresholds on the forearm were comparable between groups, and the incidence of postoperative hyperalgesia was only decreased in the peri-incisional area in the high remifentanyl (4 ng/mL) group. The present study showed that the peri-incisional area pain threshold was decreased 48 h after surgery which was reduced by nalbuphine 24 h after surgery. Hyperalgesia is a state of nociceptive sensitization and can be

Table 2 Patient Receiving Analgesics and Postoperative Stays in the PACU and Hospital

Characteristic	HRNA	HRSA	LRNA	LRSA	P value
Patient receiving analgesics (n)	7 (29.2)	15 (62.5)	6 (25)	8 (33.3)	0.0308
PACU (min)	57 (21)	58 (25)	61 (23)	62 (17)	0.8568
Length of hospital stay (days)	4 (4–5)	4 (4–5)	4 (4–4)	4 (4–5)	0.2109

Notes: PACU data are presented as mean (standard deviation), length of hospital stay (days) is median (interquartile range), and number of patients (%). HRNA, 0.4 $\mu\text{g}/\text{kg}/\text{min}$ of remifentanyl with 0.2 mg/kg of nalbuphine group; HRSA, 0.4 $\mu\text{g}/\text{kg}/\text{min}$ of remifentanyl with saline group; LRNA, 0.1 $\mu\text{g}/\text{kg}/\text{min}$ of remifentanyl with 0.2 mg/kg of nalbuphine group; LRSA, 0.1 $\mu\text{g}/\text{kg}/\text{min}$ of remifentanyl with saline group; PACU, post-anesthesia care unit.

Table 3 Postoperative Sufentanil Consumption

Sufentanil Consumption	HRNA	HRSA	LRNA	LRSA	P value	
					P1	P2
0–3 h (μg)	0 (0–5)	5 (0–10)	0 (0–0)	0 (0–9)	0.0321	0.0321
3–6 h (μg)	0 (0–0)	3 (0–5)	0 (0–0)	0 (0–5)	0.0040	0.0416
6–12 h (μg)	0 (0–0)	0 (0–5)	0 (0–0)	0 (0–0)	0.0736	0.6085
12–24 h (μg)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0.2340	1.0000
24–48 h (μg)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0.4894	1.0000

Notes: Data are presented as median (interquartile range). HRNA, 0.4 $\mu\text{g}/\text{kg}/\text{min}$ of remifentanyl with 0.2 mg/kg of nalbuphine group; HRSA, 0.4 $\mu\text{g}/\text{kg}/\text{min}$ of remifentanyl with saline group; LRNA, 0.1 $\mu\text{g}/\text{kg}/\text{min}$ of remifentanyl with 0.2 mg/kg of nalbuphine group; LRSA, 0.1 $\mu\text{g}/\text{kg}/\text{min}$ of remifentanyl with saline group. P1, HRNA vs HRSA by Mann–Whitney *U*-test; P2, LRNA vs LRSA by Mann–Whitney *U*-test.

a consequence of opioid use or due to tissue trauma and/or inflammation.¹⁶ Hyperalgesia is usually classified as primary or secondary. Primary hyperalgesia is limited to the area of the trauma or surgical incision and arises from peripheral nociceptor sensitization, which occurs as a response to a noxious stimulation. Secondary hyperalgesia is thought to originate from central sensitization to pain and usually manifests far from the damaged area. This study assessed the effect of nalbuphine on pain thresholds in two tested areas and found slight differences. The decrease of pain threshold in the forearm indicates that hyperalgesia of non-damaged tissue is mainly caused by central pain sensitization, and nalbuphine effectively prevented RIH under this circumstance. The central mechanism of RIH is largely associated with the activity and interaction of μ -opioid and NMDA receptors; excessive opioid administration induces downregulation of glutamate transporters, which in turn makes more of glutamate available for NMDA receptors, with subsequent increased NMDA activity.³ Due to the mixed pharmacology

of nalbuphine, we speculate that it may prevent RIH by initially occupying and partially antagonizing μ -receptors and simultaneously stimulating κ -receptors that have also been implicated in mitigating RIH.¹⁷ Alternatively, hyperalgesia in the peri-incision area may be affected by both peripheral and central sensitization. In this scenario, hyperalgesia of wounded tissues may originate from the sensitization of peripheral nociceptive receptors or activation of peripheral glia by surgery and/or opioid treatment to induce secretion of inflammatory mediators such as tumor necrosis factor- α and interleukin-1 β , leading to peripheral sensitization, postsurgical pain, and hyperalgesia.¹⁸ Honda et al showed that sensitization of peripheral transient receptor potential (TRP) TRP vanilloid 1 and TRP ankyrin 1 are involved in mechanical and thermal hypersensitivity,¹⁹ suggesting that peri-incisional hyperalgesia is not only due to RIH. Another study demonstrated that nalbuphine attenuates pruritus and promotes skin healing through anti-inflammatory effects.²⁰ The antihyperalgesic actions of nalbuphine on

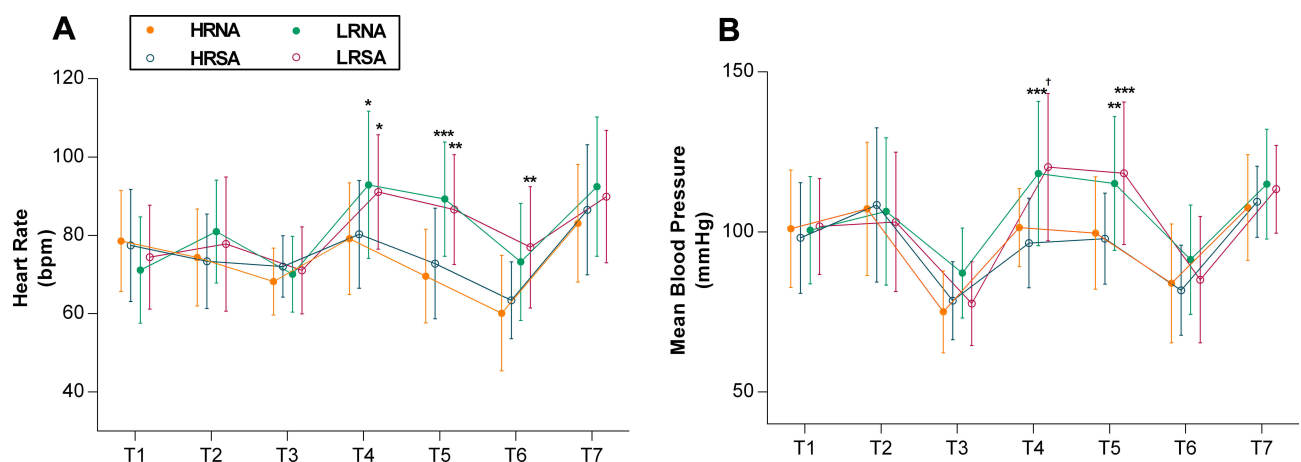


Figure 4 Heart rate (A) and mean arterial pressure (B) at different time points during surgery. Data are expressed as mean (standard deviation). HRNA, 0.4 $\mu\text{g}/\text{kg}/\text{min}$ of remifentanyl with 0.2 mg/kg of nalbuphine group; HRSA, 0.4 $\mu\text{g}/\text{kg}/\text{min}$ of remifentanyl with saline group; LRNA, 0.1 $\mu\text{g}/\text{kg}/\text{min}$ of remifentanyl with 0.2 mg/kg of nalbuphine group; LRSA, 0.1 $\mu\text{g}/\text{kg}/\text{min}$ of remifentanyl with saline group. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, † $P < 0.0001$ vs HRSA.

Table 4 Postoperative Side Effects

Adverse Events	HRNA	HRSA	LRNA	LRSA	P value
Nausea (n)	4 (16.7)	5 (20.8)	3 (12.5)	2 (8.3)	0.6431
Vomiting (n)	1 (4.2)	2 (8.3)	1 (4.2)	0 (0)	0.5546
Headache (n)	2 (8.3)	1 (4.2)	0 (0)	2 (8.3)	0.5085
Dizziness (n)	4 (16.7)	6 (25.0)	7 (29.2)	5 (20.8)	0.7580
Respiratory depression (n)	0 (0)	0 (0)	0 (0)	0 (0)	1.0000

Notes: Data are presented as number of patients (%). HRNA, 0.4 µg/kg/min of remifentanyl with 0.2 mg/kg of nalbuphine group; HRSA, 0.4 µg/kg/min of remifentanyl with saline group; LRNA, 0.1 µg/kg/min of remifentanyl with 0.2 mg/kg of nalbuphine group; LRSA, 0.1 µg/kg/min of remifentanyl with saline group.

wound tissues remain to be confirmed. Several lines of research indicate that non-steroidal anti-inflammatory drugs (NSAIDs) may be helpful because activation of spinal cyclooxygenase (COX) may play a role in the development of opioid-induced hyperalgesia. The analgesic and antihyperalgesic actions of NSAIDs are attributed to inhibition of peripheral prostaglandin synthesis in inflamed tissues, as well as COX inhibition in the central nervous system.^{10,21,22}

Postoperative hyperalgesia usually leads to higher pain scores and earlier need for rescue analgesics.²³ We found that the NRS scores and postoperative analgesic need were highest in the high-dose remifentanyl arm compared to the other groups. A recent meta-analysis including 27 studies and nearly 1500 patients showed that high intraoperative remifentanyl is associated with significant increases in acute pain at 4 and 24 h postoperatively and higher morphine requirements from the first day after surgery.²⁴ As a combined opioid agonist-antagonist, nalbuphine acts on the κ -receptor to produce analgesic and sedative effects, and it exerts μ -receptor antagonistic effects in the presence of other μ -receptor agonists.^{8,25,26} Clinical observations show the analgesic efficacy of nalbuphine is similar to morphine with only a slight respiratory depression and a capping phenomenon.²⁷ Our results demonstrate that nalbuphine can improve generalized pain postoperatively as evidence by lower NRS scores and postoperative analgesic requirements, possibly due to its modulatory action on central κ -receptors. Further studies should be carried out to elucidate the exact mechanism.

This study has some limitations. As mentioned above, the commonly accepted intra-operative practice is to administer infusions ranging from 0.1 to 0.5 µg/kg/min; doses above 0.2 µg/kg/min are likely to be associated with hemodynamic instability.²⁸ An infusion of 0.4 µg/kg/min remifentanyl was used as the high-dose in this trial, which is the most widely reported concentration to induce RIH. To avoid cardiovascular adverse events, we included only relatively healthy adults. Furthermore, we only evaluated

postoperative hyperalgesia by mechanical stimuli with von Frey filaments, although other quantitative measurements to detect opioid-induced hyperalgesia have been reported including mechanical (von Frey filament, pinprick and injection), thermal (cold pressor threshold, heat pain threshold), electrical, or other stimuli. A recent systematic review compared these measurements in 14 clinical studies and concluded that none of the methods tested was more powerful than the others.²⁹ A weakness of the present study is the lack of investigation into how dosages are related to the effects. It is possible that different doses or administration times will achieve stronger antihyperalgesic actions on RIH to the incisional area, but further research is needed.

Conclusion

Nalbuphine exerts mixed pharmacological actions on opioid receptors. It antagonizes μ -receptors but stimulates κ -receptors, which appears to be a unique property. Our results show that preemptive nalbuphine can reduce postoperative hyperalgesia induced by high-dose remifentanyl and could reduce postoperative pain and rescue analgesic consumption in patients undergoing laparoscopic cholecystectomy.

Data Sharing Statement

The data used and/or analyzed during the current study will be available for anyone who wishes to access them on reasonable request. The data will be accessible from immediately following publication to 6 months after publication via the first or the corresponding author by email.

Ethical Statement

The authors declare that all the patients provided written informed consent and that this study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Ethics Committee of the Tongling People's Hospital of Anhui University (No. 2018-12), and

was registered in the Chinese Clinical Trial Registry (ChiCTR1800020209).

Acknowledgments

The authors are grateful to the participating patients. We acknowledge Xiaohan Wang and Yingying Sui for their excellent help with patient organization and nursing assistance.

Author Contributions

Jun Hu and Ye Zhang helped with the study design, writing the original manuscript, and data analysis; Jun Hu, Shuangshuang Chen, Mudan Zhu, Ping Wang, Jinbao Chen, and Yun Wu helped with patient recruitment and data collection; Jinbao Chen and Ye Zhang helped with supervision and validation. All authors contributed to the data analysis, drafting or revising of the article, gave their final approval for the version to be published, and agreed to be accountable for all aspects of the work.

Funding

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure

There are no conflicts of interest to declare.

References

- Ljungqvist O. ERAS-enhanced recovery after surgery: moving evidence-based perioperative care to practice. *JPEN J Parenteral Enteral Nutr.* 2014;38(5):559–566. doi:10.1177/0148607114523451
- Caparlar CO, Ozhan MO, Suzer MA, et al. Fast-track anesthesia in patients undergoing outpatient laparoscopic cholecystectomy: comparison of sevoflurane with total intravenous anesthesia. *J Clin Anesth.* 2017;37:25–30. doi:10.1016/j.jclinane.2016.10.036
- Yu EH, Tran DH, Lam SW, Irwin MG. Remifentanyl tolerance and hyperalgesia: short-term gain, long-term pain? *Anaesthesia.* 2016;71(11):1347–1362. doi:10.1111/anae.13602
- Kandil TS, El Hefnawy E. Shoulder pain following laparoscopic cholecystectomy: factors affecting the incidence and severity. *J Laparoendosc Adv Surg Tech A.* 2010;20(8):677–682. doi:10.1089/lap.2010.0112
- Bisgaard T, Kehlet H, Rosenberg J. Pain and convalescence after laparoscopic cholecystectomy. *Eur J Surg.* 2001;167(2):84–96. doi:10.1080/110241501750070510
- Koo CH, Yoon S, Kim BR, et al. Intraoperative naloxone reduces remifentanyl-induced postoperative hyperalgesia but not pain: a randomized controlled trial. *Br J Anaesth.* 2017;119(6):1161–1168. doi:10.1093/bja/aex253
- De Souza EB, Schmidt WK, Kuhar MJ. Nalbuphine: an autoradiographic opioid receptor binding profile in the central nervous system of an agonist/antagonist analgesic. *J Pharmacol Exp Ther.* 1988;244(1):391–402.
- Schmidt WK, Tam SW, Shatzberger GS, Smith DH Jr., Clark R, Vernier VG. Nalbuphine. *Drug Alcohol Depend.* 1985;14(3–4):339–362. doi:10.1016/0376-8716(85)90066-3
- Cornelissen JC, Steele FF, Rice KC, Nicholson KL, Banks ML. Additive and subadditive antiallodynic interactions between mu-opioid agonists and N-methyl D-aspartate antagonists in male rhesus monkeys. *Behav Pharmacol.* 2018;29(1):41–52. doi:10.1097/FBP.0000000000000336
- Zhang L, Shu R, Zhao Q, Li Y, Yu Y, Wang G. Preoperative butorphanol and flurbiprofen axetil therapy attenuates remifentanyl-induced hyperalgesia after laparoscopic gynaecological surgery: a randomized double-blind controlled trial. *Br J Anaesth.* 2016;117(4):504–511. doi:10.1093/bja/aew248
- Zhang L, Shu R, Zhao Q, et al. Preoperative but not postoperative flurbiprofen axetil alleviates remifentanyl-induced hyperalgesia after laparoscopic gynecological surgery: a prospective, randomized, double-blinded, trial. *Clin J Pain.* 2017;33(5):435–442. doi:10.1097/AJP.0000000000000416
- Song JW, Lee YW, Yoon KB, Park SJ, Shim YH. Magnesium sulfate prevents remifentanyl-induced postoperative hyperalgesia in patients undergoing thyroidectomy. *Anesth Analg.* 2011;113(2):390–397. doi:10.1213/ANE.0b013e31821d72bc
- Celerier E, Gonzalez JR, Maldonado R, Cabanero D, Puig MM. Opioid-induced hyperalgesia in a murine model of postoperative pain: role of nitric oxide generated from the inducible nitric oxide synthase. *Anesthesiology.* 2006;104(3):546–555. doi:10.1097/0000542-200603000-00023
- Richebe P, Pouquet O, Jelacic S, et al. Target-controlled dosing of remifentanyl during cardiac surgery reduces postoperative hyperalgesia. *J Cardiothorac Vasc Anesth.* 2011;25(6):917–925. doi:10.1053/j.jvca.2011.03.185
- Kim SH, Stoicea N, Soghomonyan S, Bergese SD. Intraoperative use of remifentanyl and opioid induced hyperalgesia/acute opioid tolerance: systematic review. *Frontiers Pharmacol.* 2014;5:108. doi:10.3389/fphar.2014.00108
- Richebe P, Cahana A, Rivat C. Tolerance and opioid-induced hyperalgesia. Is a divorce imminent? *Pain.* 2012;153(8):1547–1548. doi:10.1016/j.pain.2012.05.002
- Goncalves Dos Santos G, Vieira WF, Vendramini PH, et al. Dipyrone is locally hydrolyzed to 4-methylaminoantipyrine and its antihyperalgesic effect depends on CB2 and kappa-opioid receptors activation. *Eur J Pharmacol.* 2020;874:173005. doi:10.1016/j.ejphar.2020.173005
- Matsuda M, Huh Y, Ji RR. Roles of inflammation, neurogenic inflammation, and neuroinflammation in pain. *J Anesth.* 2019;33(1):131–139. doi:10.1007/s00540-018-2579-4
- Honda K, Shinoda M, Kondo M, et al. Sensitization of TRPV1 and TRPA1 via peripheral mGluR5 signaling contributes to thermal and mechanical hypersensitivity. *Pain.* 2017;158(9):1754–1764. doi:10.1097/j.pain.0000000000000973
- Inan S, Huerta AT, Jensen LE, Dun NJ, Cowan A. Nalbuphine, a kappa opioid receptor agonist and mu opioid receptor antagonist attenuates pruritus, decreases IL-31, and increases IL-10 in mice with contact dermatitis. *Eur J Pharmacol.* 2019;864:172702. doi:10.1016/j.ejphar.2019.172702
- Malmberg AB, Yaksh TL. Antinociceptive actions of spinal nonsteroidal anti-inflammatory agents on the formalin test in the rat. *J Pharmacol Exp Ther.* 1992;263(1):136–146.
- Ye H, Lian X, Chen R, et al. Intraoperative administration of intravenous flurbiprofen axetil with nalbuphine reduces postoperative pain after orbital decompression: a single-center, prospective randomized controlled trial. *J Pain Res.* 2019;12:659–665. doi:10.2147/JPR.S187020
- Weinbroum AA. Postoperative hyperalgesia-A clinically applicable narrative review. *Pharmacol Res.* 2017;120:188–205. doi:10.1016/j.phrs.2017.02.012

24. Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *Br J Anaesth.* 2014;112(6):991–1004. doi:10.1093/bja/aeu137
25. Liang RJ, Lai YH, Kao YT, Yang TH, Chen YL, Wang HJ. A novel finding of nalbuphine-6-glucuronide, an active opiate metabolite, possessing potent antinociceptive effects: synthesis and biological evaluation. *Eur J Med Chem.* 2019;178:544–551. doi:10.1016/j.ejmech.2019.06.028
26. Cornelissen JC, Steele FF, Tenney RD, et al. Role of mu-opioid agonist efficacy on antinociceptive interactions between mu agonists and the nociceptin opioid peptide agonist Ro 64-6198 in rhesus monkeys. *Eur J Pharmacol.* 2019;844:175–182. doi:10.1016/j.ejphar.2018.12.021
27. Zeng Z, Lu J, Shu C, et al. A comparison of nalbuphine with morphine for analgesic effects and safety: meta-analysis of randomized controlled trials. *Sci Rep.* 2015;5:10927. doi:10.1038/srep10927
28. Maurtua MA, Deogaonkar A, Bakri MH, et al. Dosing of remifentanyl to prevent movement during craniotomy in the absence of neuromuscular blockade. *J Neurosurg Anesthesiol.* 2008;20(4):221–225. doi:10.1097/ANA.0b013e3181806c4a
29. Katz NP, Paillard FC, Edwards RR. Review of the performance of quantitative sensory testing methods to detect hyperalgesia in chronic pain patients on long-term opioids. *Anesthesiology.* 2015;122(3):677–685. doi:10.1097/ALN.0000000000000530

Journal of Pain Research

Dovepress

Publish your work in this journal

The Journal of Pain Research is an international, peer reviewed, open access, online journal that welcomes laboratory and clinical findings in the fields of pain research and the prevention and management of pain. Original research, reviews, symposium reports, hypothesis formation and commentaries are all considered for publication. The manuscript

management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/journal-of-pain-research-journal>