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ORIGINAL SCIENTIFIC REPORT

# Comparison Between Preoperative and Intraoperative Administration of Nefopam for Acute and Chronic Postoperative Pain in Colon Cancer Patients: A Prospective, Randomized, Double-Blind Study

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## Abstract

*Background* The present study was designed as a prospective, randomized, double-blind clinical trial to evaluate the effects of preoperatively administered nefopam on postoperative acute hyperalgesia and the long-term painful sequelae compared to intraoperative administration.

*Methods* One hundred and fifty patients undergoing elective laparoscopic colectomy were enrolled. Group 1 (post-incisional nefopam) patients received saline at 30 min before skin incision followed by intraoperative administration of 20 mg nefopam at 1 h after incision. Group 2 (pre-incisional nefopam) patients were administered 20 mg nefopam before skin incision and received saline after skin incision. At postoperative 2, 6, 24, 48, and 72 h, fentanyl consumption and pain intensities at rest and during deep breathing were evaluated by visual analog scale (VAS). The incidence of the long-term painful sequelae after surgery was evaluated more than one year after surgery.

*Results* Cumulative fentanyl consumption during postoperative 72 h was similar between Group 1 and Group 2 (1534 ± 698 μg, 95% CI 1367–1702 μg vs. 1442 ± 721 μg, 95% CI 1266–1618 μg, $P = 0.197$). VAS pain scores at rest were comparable between the two groups, but VAS scores during deep breathing were significantly lower in Group 2 than in Group 1. Six and five patients complained of mild pain (pain rating 1) at the surgical site in Group 1 and 2, respectively.

*Conclusions* Preoperatively administered nefopam reduced exertional pain compared to intraoperative administration although postoperative analgesic consumption was similar between two groups. It may be helpful to conduct early ambulation and deep breathing during the acute postoperative period in patients undergoing intestinal surgery.

*Trial registration No*: KCT0001656.

## Introduction

Although the incidence and severity of postoperative pain levels vary by analgesic technique, 40 to 75% of surgical patients experience moderate-to-extremely severe pain during the immediate postoperative period [1, 2]. In patients who experience inadequately treated postoperative pain after major surgery, postoperative pain is associated with increased morbidity, delayed recovery time, functional impairment, and higher healthcare costs. In addition, inadequately treated acute postoperative pain can sensitize and imprint indelibly on the central nervous system (CNS). These changes in the CNS may initiate the development of acute postoperative hyperalgesia that increases postoperative pain and larger opioid requirement. Furthermore, acute postoperative hyperalgesia may initiate the development of the long-term painful sequelae [3–5]. Because therapeutic modalities for the long-term painful sequelae after surgery

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are limited, prevention of initial sensitization and imprinting of the CNS is considered the best way to alleviate the long-term painful sequelae after surgery.

Preemptive analgesia is a modality for postoperative pain management that initiates analgesia preoperatively to prevent sensitization of the CNS by pain signals evoked by surgical tissue damage [6, 7]. Because preemptive analgesia prevents initial pain transmission on the nociceptive system, it can potentially be more effective in preventing the development of acute postoperative hyperalgesia and the long-term painful sequelae after surgery compared to conventional analgesia that is initiated postoperatively. Central sensitization by the transmission of pain signals on the nociceptive system includes the excitatory amino acids aspartate and glutamate, and substance *P*, which acts on *N*-methyl-D-aspartate (NMDA) and 2-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors [6–8].

Nefopam hydrochloride is a non-opioid, centrally acting antinociceptive compound that has been widely used as a postoperative analgesic in Europe and Asia [9]. Although its exact mechanism of action remains unclear, nefopam inhibits monoamine reuptake [4, 10, 11] and blocks voltage-sensitive calcium and sodium channels [12, 13]. These actions lead to decreased activation of postsynaptic receptors. Consequently, nefopam could modulate postsynaptic glutamatergic receptors, such as NMDA receptors [12–14], which are involved in the development of postoperative acute hyperalgesia and the long-term painful sequelae [15]. Therefore, nefopam has the potential to control acute postoperative pain and hyperalgesia via these mechanisms [16]. The authors hypothesized that preoperatively administered nefopam has the effects on postoperative acute hyperalgesia and the long-term painful sequelae compared to intraoperative administration.

The present study was designed to evaluate the effects of preoperatively administered nefopam on postoperative acute hyperalgesia and the long-term painful sequelae compared to intraoperative administration after laparoscopic colectomy.

## Material and methods

The present study was a prospective, randomized, double-blind, parallel designed clinical trial. The study was registered with the WHO International Clinical Trials Registry Platform (KCT0001656) after approving by the Institutional Review Board of Chonbuk National University Hospital (CUH 2013-01-009). The manuscript was described according to CONSORT 2010 checklist. Written informed consent was obtained from all participants. A total of 150 adult patients undergoing elective laparoscopic colectomy due to colon cancer were enrolled in the study. Patient exclusion criteria were as follows: current medication with monoamine oxidase inhibitors, analgesics, sedatives, or antidepressants, medical history of seizure, myocardial infarction, urinary retention, angle-closure glaucoma, and hypersensitivity to nefopam or fentanyl, pregnancy or lactation, or inability to understand the use of a patient-controlled analgesia (PCA) device.

At preanesthetic visit, patients were instructed the visual analog scale (VAS) (where 0 indicates "no pain" and 10 indicates "worst pain imaginable") for pain and how to operate the PCA device (Accumate 1100®, Wooyoung Meditech, Seoul, Korea). Preoperative pulmonary function tests (PFT) including forced expiratory volume in 1 s ($FEV_1$) and forced vital capacity (FVC) were examined using a portable spirometry (Contec® spirometer, Contec Medical System Co. Qinhuangdao, China). The researcher (SK) randomly assigned the subjects using a computer-generated block randomization scheme with four-block size to one of two groups (allocation ratio 1:1, https://randomization.com). The allocation sequence was concealed from the researchers (HL and BK) enrolling and assessing participants in sequentially numbered, opaque, sealed envelopes. On the morning of surgery, a nurse not involved in the study prepared two types of 50-mL saline bottles. One bottle contained 20 mg nefopam (Acupan®, Biocodex, France) and the other (placebo) did not. The nefopam and placebo bottles were identical in appearance. They were consecutively numbered by the nurse for each subject according to the randomization schedule. Group 1 (post-incisional nefopam, control group) patients received 50 mL saline at about 30 min before skin incision followed by intraoperative administration of 20 mg nefopam in a 50-mL saline bottle at 1 h after incision. Group 2 (pre-incisional nefopam, experimental group) patients were administered 20 mg nefopam in a 50-mL saline bottle at about 30 min before skin incision and received only saline at 1 h after skin incision.

After placement of standard anesthetic monitoring, all patients received same anesthetic techniques with sevoflurane and remifentanil. Baseline heart rate, arterial pressure, and bispectral index (BIS) value were measured immediately before induction. Anesthesia was induced with 1.5–2.0 mg/kg propofol and 1.0 mg/kg rocuronium. Remifentanil (50 μg/mL, Ultiva®, GlaxoSmithKline, Parma, Italy) was administered using a Minto model effect-site target-controlled infusion pump. Blood pressure was maintained within 20% of preanesthetic values by adjustment anesthetic concentration. The patients were monitored for nefopam-related complications including sweating and tachycardia for 2 h at the post-anesthesia care unit.

An intravenous (IV) PCA device containing fentanyl 2000 μg in 80 mL was equipped for 72 h. The patients were administered 2 μg/kg fentanyl as loading dose and 0.3 mg ramosetron for prevention of postoperative nausea and vomiting (PONV) at skin closure. Adjunctive postoperative analgesics were not allowed. PCA was set with 0.5 mL/h (fentanyl 12.5 μg/h) continuous background infusion, 1 mL (fentanyl 25 μg) demand bolus dose, 6 min lockout interval.

The primary purpose of the current study was to compare fentanyl consumption and pain intensity during postoperative 72 h between preoperative and intraoperative administration of nefopam. The postoperative fentanyl consumption and pain intensity were evaluated at 2, 6, 24, 48, and 72 h after operation. Postoperative pain intensity was evaluated at rest and during deep breathing for examination of pulmonary function. The secondary purpose was incidence of the long-term painful sequelae after surgery. The incidence of the long-term painful sequelae after surgery was evaluated by structured telephone interview more than one year after surgery. Pain remaining at rest around surgical scars was rated between 0 (no pain), 1 (mild pain), 2 (moderate pain), and 3 (severe pain, needed to be treated with analgesics). An anesthesiologist who was blinded to subject group assignment evaluated the postoperative fentanyl consumption, VAS pain score, and the incidence of the long-term painful sequelae to exclude inter-rater bias. The postoperative PFTs were examined at each time point. The side effects of fentanyl were recorded including nausea, vomiting, somnolence, pruritus, urinary retention, and respiratory depression.

### Statistical analysis

The sample size estimate was based on the expected difference in mean fentanyl consumption during the postoperative 72 h between the post-incisional and pre-incisional nefopam groups. Fentanyl consumption during the postoperative 72 h, which was the primary endpoint, was 1550 ± 875 μg in our pilot study of 10 patients who received nefopam post-incisionally. In clinical trials about postoperative analgesic consumption, generally 10 to 30% of the differences between the groups is acceptable. Because the standard deviation was too large and the postoperative pain and analgesic consumption were highly subjective experience, the authors decided > 500 μg (≈30%) as clinically significant difference. To obtain a difference in 500 μg average fentanyl consumption and 875 μg expected standard deviation with $\alpha = 0.05$ and $\beta = 0.10$, 66 patients are required in each group. The sample size was decided to be 150 patients considering lost to follow-up.

SigmaPlot 13.0 (Systat Software Inc. San Jose, USA) was used for statistical analysis. Data are presented as the mean and standard deviation or median and interquartile range. Clinical characteristics of the patients were analyzed with Student's t tests or Chi-square tests. Fentanyl consumption, pain intensity, and PFTs were compared with two-way repeated measures of ANOVA and Holm-Sidak method for post hoc test. The incidences of long-term painful sequelae after surgery and side effects of fentanyl use were analyzed using Chi-square tests. A $P$ value less than 0.05 was regarded as significant.

## Results and discussion

Of the 150 allocated surgical patients, six patients who underwent laparotomy and eight patients with fentanyl side effects including severe PONV were excluded from the 72-h follow-up postoperative pain and fentanyl consumption analysis. The clinical characteristics of the patients are presented in Table 1. Of the remaining 136 patients, 12 patients in each group were lost to the long-term follow-up of painful sequelae after surgery by telephone interview (Fig. 1).

There were no differences in fentanyl consumption between the two groups at postoperative 2, 6, 24, 48, and 72 h (Fig. 2). Cumulative fentanyl consumption during postoperative 72 h were similar between Group 1 and Group 2 (1534 ± 698 μg, 95% confidence interval 1367–1702 μg vs. 1442 ± 721 μg, 95% confidence interval 1266–1618 μg, $P = 0.197$) (Fig. 2). VAS pain scores at rest were comparable between the two groups, but VAS scores during deep breathing were significantly lower in Group 2 than in Group 1 at the time of each examination (Table 2).

PFTs gradually increased after operation. At postoperative 72 h, FVC and $FEV_1$ were 82% and 82 to 86% of preoperative values, respectively. There were no significant differences in FVC and $FEV_1$ between the two groups for each measurement (Fig. 3).

No patient showed nefopam-related complications. Seven patients discontinued PCA use due to complications of fentanyl. Five of these patients complained of severe PONV and one patient suffered from dizziness and urinary retention.

Six patients in Group 1 and five patients in Group 2 complained of mild pain (pain rating 1) at the surgical site in a telephone interview ($P = 0.950$). No patients complained of more than moderate pain ( ≥ pain rating 2) in both groups.

The present study prospectively examined whether preoperatively administered nefopam (20 mg) has effects on the development of acute postoperative hyperalgesia

**Table 1** Demographic and clinical characteristics

| | Group 1 ($N$ = 69) | Group 2 ($N$ = 67) | $P$ values |
|---|---|---|---|
| Age (years) | 58.7 ± 10.2 | 57.9 ± 9.9 | 0.636 |
| Gender (F/M) | 26/43 | 26/41 | 0.967 |
| Height (cm) | 162.7 ± 8.3 | 164.0 ± 7.8 | 0.342 |
| Weight (kg) | 63.9 ± 10.9 | 65.1 ± 10.2 | 0.536 |
| Operation time (min) | 114.8 ± 28.9 | 113.6 ± 40.5 | 0.852 |
| Anesthesia time (min) | 165.7 ± 31.2 | 160.6 ± 41.3 | 0.412 |
| *Types of operation* | | | |
| Anterior resection | 32 | 33 | 0.951 |
| Lower anterior resection | 17 | 17 | |
| Lt. hemicolectomy | 3 | 4 | |
| Rt. hemicolectomy | 16 | 12 | |
| Subtotal colectomy | 1 | 1 | |

and the long-term postoperative painful sequelae compared to intraoperative nefopam. In the current study, the authors found a unique result that preoperative nefopam patients showed lower pain scores during forced expiration at postoperative 2, 24, 48, and 72 h compared to the intraoperative nefopam group, although both groups consumed a similar dose of fentanyl using an IV-PCA and experienced similar pain intensity at rest. Most previous postoperative pain management studies examined pain scores at rest and analgesic consumption, but might have not examined exertional pain scores. We examined FVC and $FEV_1$ using a portable pulmonary function test device and evaluated pain scores during forced expiration. Reduced pain intensity during forced expiration or exercise is very important in surgical patients, especially intestinal surgery. It can make early ambulation, deep breathing, and coughing, therefore preventing postoperative complications, including paralytic ileus and atelectasis. Consequently, patients with low exertional pain facilitate early recovery, low complication incidence, and decreased hospital stays.

Preoperatively administered nefopam reduced exertional pain during acute postoperative pain in the current study. This result was not discovered in previous studies with NMDA receptor antagonists, including ketamine and nefopam. A previous study reported preoperative epidural analgesia decreased functional exercise capacity at 3 and 6 weeks after surgery compared to postoperative analgesia using an IV-PCA [17]. Although the results cannot differentiate the effects between epidural analgesia and preoperative analgesia, the cumulative results may provide a valuable clue. Therefore, future studies are required to evaluate the relationship between prevention of nociceptive transmission and exertional pain or functional exercise capacity.

In our results, exertional pain scores were lower in the preoperative nefopam group compared to the intraoperative nefopam group, but analgesic consumption, pain scores at rest, and the incidence of chronic pain were not different between the two groups. These results are different from a previous study in breast cancer surgery [18]. The study reported preoperatively administered 20 mg of nefopam reduced acute postoperative pain, analgesic requirement, and the incidence of chronic pain. The discrepancy in acute postoperative pain and analgesic requirement between our results and the previous study may be due to the non-equianalgesic setting. Control patients did not receive nefopam intraoperatively or postoperatively; they received only saline as the placebo in the previous study. The elimination half-life of nefopam is 3 to 8 h and its active metabolite is 10–15 h [19]. Therefore, preoperative 20 mg of nefopam could affect pain intensity at both the intraoperative and acute postoperative periods after about a 70 min operation. Additionally, the previous study evaluated the incidence of chronic pain development at 3 months after operation, but we examined pain more than one year after operation. The examination timing of the long-term painful sequelae may have affected the results.

For preemptive analgesia in surgical patients, analgesic interventions capable of preventing central sensitization were used throughout the perioperative period. An inadequate blockade of pain transmission cannot be preemptive, even if analgesia is provided before the surgical incision. Preemptive may not simply mean “before incision” [20]. However, complete blockade of surgical pain throughout the perioperative period with systemic analgesics is difficult in clinical practice. Because central sensitization by the transmission of pain signals on the nociceptive system includes NMDA receptors [6–8], preemptive analgesia with systemic NMDA receptor antagonists, theoretically, should be effective in preventing the development of acute postoperative hyperalgesia and the long-term painful sequelae. Ketamine and dextromethorphan are NMDA

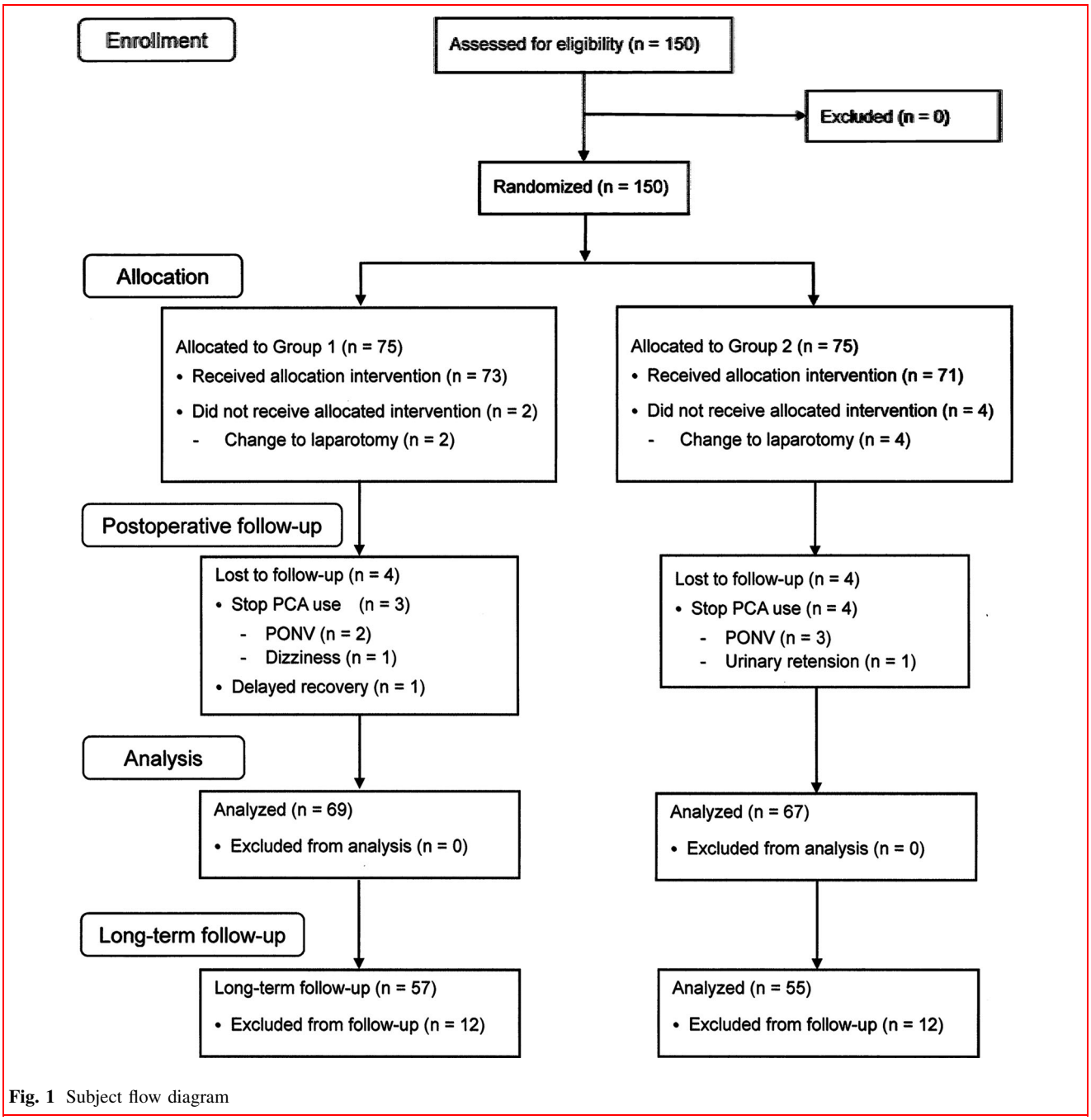


**Fig. 1** Subject flow diagram

receptor antagonists at doses that are not directly analgesic and have the ability to block central sensitization. However, the preemptive analgesic effects of ketamine and dextromethorphan were inconsistent in human clinical studies [20–23]. Therefore, the authors would like to examine whether preoperatively administered analgesic nefopam might be helpful in reducing acute and chronic postoperative pain because nefopam can modulate NMDA receptors. However, 20 mg of nefopam did not reduce acute and chronic postoperative pain, which was different from our prediction. These results were similar to studies that demonstrated negative preemptive analgesic effects with low dose ketamine.

Although the exact analgesic mechanism of nefopam remains unknown, IV nefopam quickly produces potent inhibition of the nociceptive reflex and provides 30 to 50% of morphine-sparing effects when given to surgical patients [24]. Nefopam 20 mg is equipotent with morphine 6 to 12 mg [25, 26]. Although the usual IV dose of nefopam is 20 mg, the median effective dose ($ED_{50}$) and effective dose

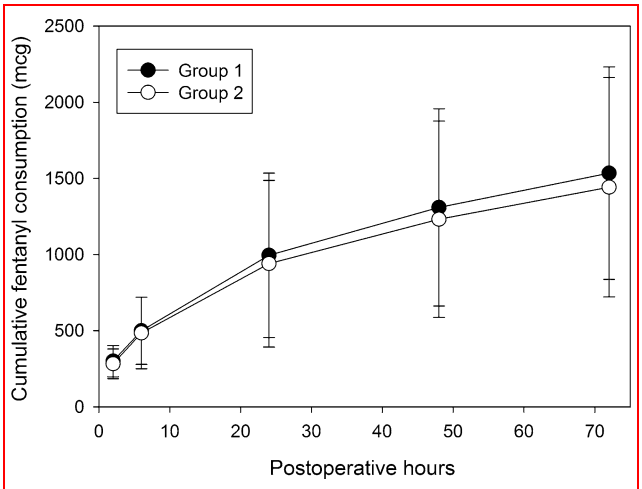


**Fig. 2** Cumulative fentanyl consumption was not different between Group 1 (post-incisional nefopam, control group) and Group 2 (pre-incisional nefopam, experimental group) at postoperative 2, 6, 24, 48, and 72 h

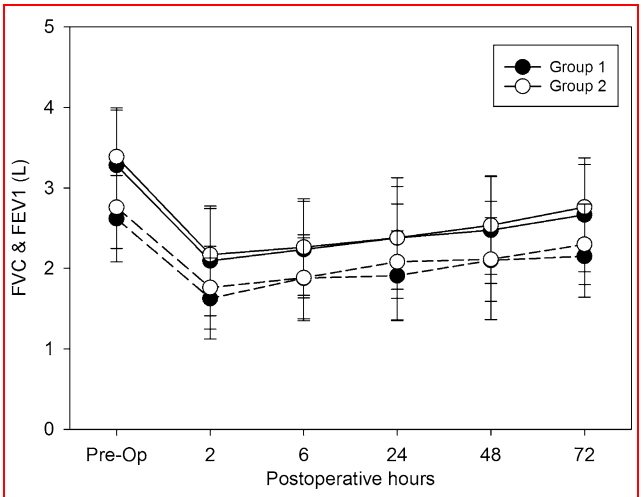


**Fig. 3** There were no significant differences between both groups in functional vital capacity (FVC) and forced expiratory volume in 1 s ($FEV_1$). FVC and $FEV_1$ decreased after operation and increased gradually afterward. Compared to preoperative values, FVC and $FEV_1$ recovered to 82% and 82 to 86% at postoperative 72 h, respectively. There were no significant differences in FVC and $FEV_1$ between the two groups for each measurement

**Table 2** Postoperative visual analog pain scores at rest and during deep breathing

| | | Group 1 | Group 2 |
|---|---|---|---|
| 2 h | Rest | 4.4 ± 2.1 | 3.6 ± 1.9 |
| | Deep breathing | 5.5 ± 2.1 | 4.6 ± 2.0* |
| 6 h | Rest | 3.1 ± 1.7 | 2.7 ± 1.8 |
| | Deep breathing | 4.1 ± 2.0 | 3.4 ± 1.9* |
| 24 h | Rest | 2.6 ± 1.8 | 2.2 ± 1.7 |
| | Deep breathing | 3.6 ± 1.8 | 2.9 ± 1.8* |
| 48 h | Rest | 2.0 ± 1.6 | 1.7 ± 1.5 |
| | Deep breathing | 2.8 ± 1.8 | 2.1 ± 1.8* |
| 72 h | Rest | 1.6 ± 1.6 | 1.2 ± 1.3 |
| | Deep breathing | 2.2 ± 1.8 | 1.5 ± 1.4* |

*$P < 0.05$

in 80% ($ED_{80}$) of the patients suffering from moderate pain in the postoperative period were 28 mg and close to 60 mg, respectively. Therefore, 20 mg of nefopam used in the current study might not be enough to adequately prevent nociceptive transmission and neuronal plasticity. The authors thought that the dosage was an important reason for the inconsistent results.

The current study has two limitations. First, the dosage used in the current study was insufficient as mentioned above. Although 20 mg of nefopam is the usual IV dose and recommended by manufacturer, the dose is too low to prevent nociceptive transmission and neuronal plasticity during intraoperative and postoperative periods in patients suffering from moderate to severe pain. Second, we used only telephone interviews to evaluate the long-term postoperative painful sequelae. In clinical trials to evaluate anti-hyperalgesic effects, physical examinations might be implemented to test hyperalgesia and allodynia. A more meticulous physical examination is required to test painful sequelae even though these examinations are more difficult to obtain one year after surgery. Therefore, further studies are required to evaluate the effects of nefopam at a dose of more than 20 mg on anti-hyperalgesia and postoperative exertional pain intensity, and functional exercise capacity.

In conclusion, preoperatively administered nefopam reduced exertional pain compared to intraoperative administration although postoperative analgesic consumption was similar between two groups. It may be helpful to conduct early ambulation and deep breathing during the acute postoperative period in patients undergoing intestinal surgery.

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**Compliance with ethical standards**

**Conflict of interest** All authors have no conflicts of interest.Informed ConsentInformed consent was obtained from all individual participants.

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