

Median effective dose of nefopam to treat postoperative pain in patients who have undergone laparoscopic cholecystectomy

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Abstract

Objective: Nefopam is thought to reduce postoperative pain; however, the evidence is insufficient. The recommended dose is 20 mg, and the median effective dose (ED₅₀) in the surgical setting reportedly ranges from 17 to 28 mg. However, nefopam frequently produces inadequate postoperative analgesia. We evaluated the ED₅₀ of nefopam as a single agent in patients undergoing laparoscopic cholecystectomy.

Methods: Twenty-nine patients were scheduled for laparoscopic cholecystectomy. Postoperative pain was evaluated using a numerical pain scale (NPS). When the NPS score was >3, patients were administered a predetermined dose of nefopam. The dose was calculated using the up-and-down allocation technique based on the previous response. The initial dose was 28 mg, with adjustment intervals of 5 mg. An effective response was defined as a decrease in the NPS score to <3 at 30 minutes after infusion.

Results: The ED₅₀ of nefopam was 62.1 mg (95% confidence interval, 52.9–72.9 mg). Eight patients reported pain upon injection, and three were excluded due to severe injection pain and phlebitis.

Conclusions: The estimated ED₅₀ was higher than the predetermined dose based on previous studies. We recommend that the dose of nefopam be chosen after careful consideration of individual variations and clinical settings.

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Keywords

Nefopam, median effective dose, pain, postoperative, cholecystectomy, numerical pain scale

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Background

Nefopam is an analgesic agent with a unique mechanism of action—it is classified as a centrally acting, nonopioid analgesic. The drug inhibits receptors that are associated with serotonin, norepinephrine, and dopamine reuptake.¹ Nefopam has been used to treat acute and chronic pain in the clinical setting. However, whether the use of nefopam is warranted by evidence remains unclear. Most clinical trials have investigated the opioid-sparing effects of nefopam, but results are still inconsistent in this regard.^{2,3} Furthermore, one study revealed that there is insufficient evidence showing that nefopam is a useful nonopioid analgesic in surgical patients.⁴

In the surgical setting, the median effective dose (ED50) and 80% effective dose (ED80) of nefopam are reportedly 27.4 and 74.4 mg, respectively, for the treatment of moderate pain.⁵ However, some authors have reported that a smaller nefopam dose would be adequate to reduce the need for opioids in such settings.⁶ No consensus regarding the most effective analgesic dose across various surgical procedures has been established.

The purpose of the present study was to clarify the effective dose of nefopam and thus ensure adequate postoperative treatment using a single pain agent in patients undergoing moderate pain-inducing surgery.

Methods

Before the study, appropriate institutional review board approval (KUGH13055) and written informed consent were obtained.

This trial was also registered at a clinical research information service (<https://cris.nih.go.kr/>, KCT0002766).

Patients

Patients with an American Society of Anesthesiologists physical status of I or II and age of 20 to 65 years were enrolled. All patients were scheduled to undergo elective laparoscopic cholecystectomy. The exclusion criteria were as follows: history of convulsions or epilepsy, liver or kidney disease, coronary artery disease, urinary obstructive disease, pregnancy, complications during surgery (intraoperative bleeding, need for adhesiolysis, severe inflammation around gall bladder, etc.), administration of intravenous patient-controlled analgesia, and postoperative pain with a score of ≤ 3 on a numerical pain scale (NPS).

Anesthesia and surgical procedure

Midazolam and glycopyrrolate were administered as premedication. All patients received general anesthesia by injection of thiopental (Pentotal sodium; JW Pharmaceutical, Seoul, Republic of Korea) or propofol (Freefol-MCT; Daewon Pharmaceutical Co., Seoul, Republic of Korea) and desflurane (Suprane solution; Baxter Healthcare, Guayama, Puerto Rico). Injection of rocuronium (Esmeron; MSD Korea Ltd., Seoul, Republic of Korea) was used as a neuromuscular block. The opioid used was remifentanyl (Ultiva; GlaxoSmithKline, Brentford, UK), which was administered by continuous infusion at

a dose of 0.05 to 0.08 $\mu\text{g}/\text{kg}/\text{min}$ during anesthesia maintenance.

All surgery was performed by the same surgeon, who conducted a standardized, three-port laparoscopic cholecystectomy with adequate pneumoperitoneum. At the end of surgery, all anesthetics and remifentanyl were discontinued, and appropriate recovery from muscle relaxants was confirmed using train-of-four monitoring. Injections of glycopyrrolate and pyridostigmine were used to reverse the residual neuromuscular blocker effects. The patients were then transferred to the post-anesthetic care unit.

Study protocol

The day before surgery, the patients were taught how to use the NPS to describe their pain. The NPS was an 11-point numerical scale from 0 (no pain) to 10 (worst pain imaginable). Pain was assessed immediately after surgery and every time the patient complained of any pain. All pain assessments were carried out by a single anesthesiologist who had not participated in any previous procedures, including general anesthesia. When the NPS score was >3 , the patient was included in the study, and a slow infusion of nefopam was started immediately (Acupan; Biocodex, Gentilly, France). Patients received 20 mL of nefopam over 10 minutes as a continuous intravenous infusion, followed by 10 mL of saline over 5 minutes by a syringe pump (Injectomat TIVA Agilia; Fresenius Kabi, Bad Homburg, Germany). The dose of nefopam was calculated for each patient using the up-and-down allocation technique on the basis of their previous responses.⁷ A decrease in the NPS score to <3 was regarded as an effective response. Patients initially received 28 mg of nefopam; their next dose was increased or decreased by 5 mg according to the results of the previous dose. The initial dose and dosing interval were

based on estimates from a previous study.⁸ We re-evaluated the NPS score 30 minutes after the end of nefopam infusion. If the patients complained of pain with an NPS score of >3 , they were administered 1 $\mu\text{g}/\text{kg}$ of fentanyl (fentanyl citrate; Hana Pharm Co., Ltd., Seoul, Republic of Korea).

The possible adverse effects of nefopam and opioids include tachycardia, bradycardia, hypotension, nausea, vomiting, sedation, respiratory depression, sweating, confusion, urinary retention, itching, shivering, dry mouth, and injection site pain during infusion. These symptoms were recorded every 10 minutes from the beginning of nefopam infusion until the patients were discharged from the post-anesthetic care unit.

Statistical analysis

Statistical analysis was performed to estimate the ED₅₀ of nefopam using the up-and-down method described in Dixon's statistical analysis.^{7,9,10} This constitutes an analysis of sensitivity data that have an "all-or-none" response (NPS score of ≤ 3 or >3). The experiment was continued until the patients had shown seven deflections in accordance with previously established recommendations.^{7,9,10} We calculated the ED₅₀ of nefopam as well as its 95% CI using GraphPad Prism 5 for Windows (ver. 5.01; GraphPad Software Inc., San Diego, CA, USA). All data are presented as mean \pm standard deviation, number (percentage), or median (25%–75% quartiles). Because the NPS is not a continuous scale, the Wilcoxon signed-rank test was applied to analyze these data. All P-values of <0.05 were considered statistically significant.

Results

Twenty-nine patients were enrolled. The patients' demographic data (age, sex, body

weight, and anesthesia time) are listed in Table 1. Among the 29 patients recruited, 3 were excluded due to severe pain upon injection and subsequent phlebitis. The NPS scores immediately before nefopam infusion and 30 minutes later are shown in Figure 1. There were 7 effective and 19 ineffective responses. The mean initial NPS score was 6 (5–7.3), and it decreased to 5 (3–6) after nefopam administration ($P < 0.001$). The individual NPS score

changes are also presented in Figure 1. The estimated ED50 of nefopam was 62.1 mg (95% CI, 52.9–72.9 mg). The distribution of the effective and ineffective responses is shown in Figure 2.

Two patients (7.7%) reported mild nausea, but these symptoms had been present before nefopam administration and did not worsen after administration. Eight patients (27.59%) reported pain upon injection; however, five of these patients had an NPS score of < 3 for this pain and were not excluded. Three patients were excluded because they complained of severe injection pain during nefopam administration (NPS score of > 3 points); one of them developed acute phlebitis around the intravenous catheter placement site. When severe injection pain (NPS score of > 3) was noted, the nefopam infusion was immediately stopped, and other analgesics, along with hydration,

Table 1. Demographic data in the 26 patients

Variables	Values
Age, years	44.1 ± 9.5
Female sex	16 (61.54%)
Weight, kg	66.5 ± 9.0
Anesthesia duration, min	60.6 ± 15.2

Data are expressed as n (%) or mean ± standard deviation.

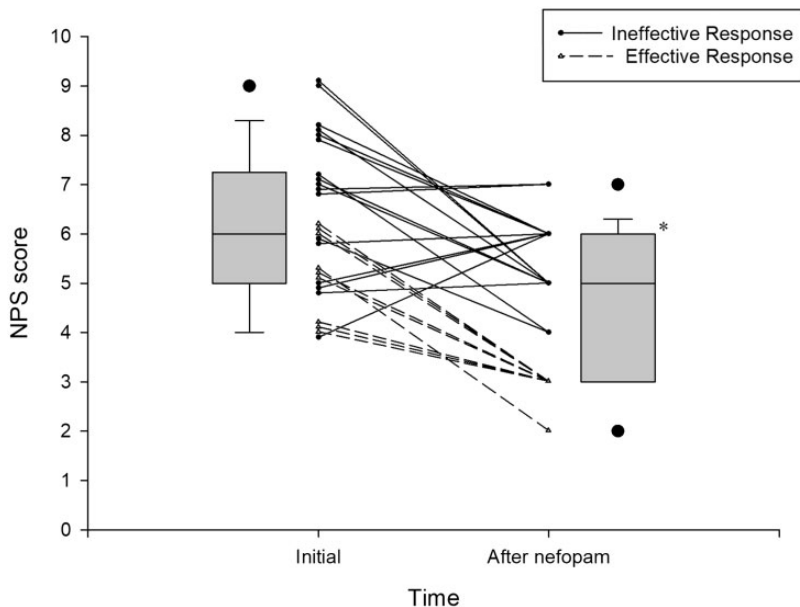


Figure 1. Pain was measured using a numerical pain scale (NPS) before and after nefopam administration. The box and whisker plot represents the median and 25%–75% quartiles of the measured NPS scores. The small black circle and straight line indicate NPS score changes in patients with an ineffective response, while the small empty triangle and dashed line indicate NPS score changes in patients with an effective response before and after nefopam administration. * $P < 0.05$

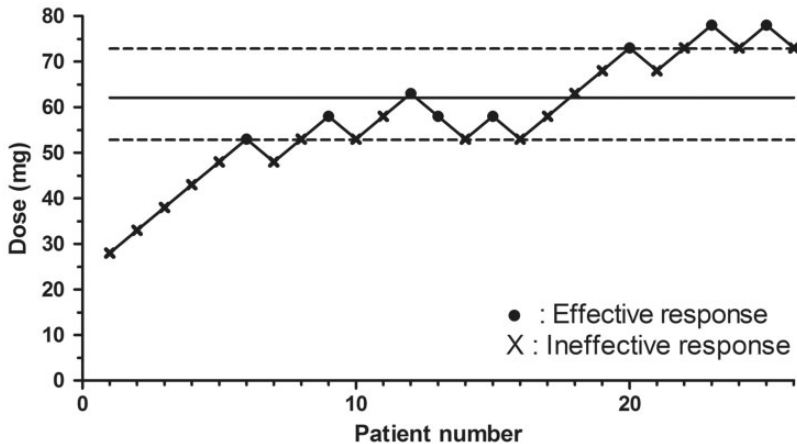


Figure 2. The distribution of effective and ineffective responses after nefopam administration. Dixon's up-and-down sensitivity analysis method was used to calculate the 50% effective dose (ED₅₀) and its 95% confidence interval (CI). The estimated ED₅₀ was 62.1 mg (95% CI, 52.9–72.9 mg). Pain was measured using a numeric pain scale (NPS) ranging from 0 to 10, and the drug was defined as effective (NPS score of ≤ 3) or ineffective (NPS score of >3). Black circles represent the effective responses, while crosses show the ineffective responses. The ED₅₀ is denoted by a horizontal line and its 95% CIs by dashed lines

were administered. In the patient who developed phlebitis, symptoms and signs gradually resolved within 1 hour. The dose of nefopam in the three excluded patients was either 53 or 68 mg; the patient who developed phlebitis received 53 mg of nefopam. Otherwise, no adverse reaction to nefopam was observed.

Discussion

The main finding of this study is that the estimated ED₅₀ of nefopam as a sole agent is close to 60 mg in postoperative patients who have undergone laparoscopic cholecystectomy. This is higher than most recommendations.^{3,6} Because the ED₅₀ is defined as the dose required to achieve 50% of the desired response in 50% of the population, the effective dose for most patients will be much higher than 60 mg.

Nefopam is a centrally acting nonopioid analgesic. When it was first introduced as an analgesic, 20 mg of nefopam was considered equipotent to 12 mg of morphine.^{11,12}

However, the pharmacokinetic properties of nefopam have been revised in recent years. The ED₅₀ of nefopam reportedly ranges from 17 mg (95% CI, 15.4–18.6 mg) to 28 mg (95% CI, 17–39 mg), and its estimated ED₈₀ is 74.4 mg.^{5,8,13} In these studies, the researchers administered nefopam over 15 to 20 minutes via a continuous intravenous route and evaluated the NPS score 30 to 45 minutes after the beginning of drug infusion. However, most of the patients were undergoing minor ear, nose, and throat surgery, for which pain is generally milder than in laparoscopic cholecystectomy.¹⁴

Several studies have shown that a cumulative dose of nefopam of up to 120 mg can reduce morphine consumption during the 24 hours immediately after surgery in patients who have undergone a major operation.^{6,15,16} However, a systemic review including all of these studies found that there is insufficient evidence for the effect of nefopam in surgical patients. Most studies concerning the analgesic effect of

nefopam have reported its synergism with other analgesics,^{6,8,15–18} while one reported that intraoperative nefopam infusion is effective during laparoscopic cholecystectomy.¹⁹ The researchers administered 0.3 mg/kg of nefopam as a bolus dose during anesthesia induction; they then continued at a dose of 65 µg/kg/h during surgery. Pain was measured using a visual analog scale and scored at around 3 during the immediate postoperative period. Continuous nefopam administration via patient-controlled analgesia produced analgesic effects that were not inferior to those of morphine and ketorolac-based patient-controlled analgesia.²⁰

In the present study, the ED₅₀ of a single dose nefopam in patients with moderate pain was 62.1 mg (95% CI, 52.9–72.9 mg). This is higher than previously reported ED₅₀ values. The difference may be due to the analgesic potency of nefopam against strong pain stimuli and to its wide interindividual variations. Several studies have shown that a wide range of opioids have cumulative effects when consumed with nefopam and that the distribution of the NPS score is skewed after nefopam administration in patients who have also been treated using opioids.^{2,6,21,22} Because the present study included only one kind of surgical procedure, the interindividual pharmacodynamic variation of nefopam emerged more clearly than in other studies. Unfortunately, the differences between a single dose and continuous infusion of nefopam have not been clearly evaluated.^{4,23} In previous evaluations, a single dose was not distinguished from continuous infusion.

Nefopam does not have a respiratory depressive effect.²⁴ The adverse reactions to nefopam are tachycardia, nausea, dizziness, and hyperhidrosis.^{21,25} In the present study, six patients received a single dose of nefopam at >68 mg, and none of these adverse reactions occurred, although three

patients experienced pain upon injection and phlebitis at an even lower dose of nefopam (53 or 68 mg). Such reactions have been reported previously, although rarely.²⁶ Because the present study was the first to include administration of a large single dose of nefopam, the pain on injection and phlebitis may have been related to the quantity of nefopam administered. Further investigation is required to determine the occurrence of pain on injection and phlebitis according to the administration dose of nefopam.

This study had some limitations. First, the up-and-down method for estimating ED₅₀ is widely used in pharmacologic research to minimize the number of patients who show an ineffective response.²⁷ The small sample size without randomization was a major statistical weak point in the present study, and bias resulting from the small sample size cannot be completely excluded. In fact, according to the Mann–Whitney rank sum test, different distributions of the NPS scores may have existed between the effective and ineffective doses in the present study (NPS score = 7 [5.5–8] in patients who were given an ineffective dose and 5 [4–6] in patients who were given an effective dose; $U = 24.0$, $P = 0.004$, effect size $\hat{p} = 0.16$) (Figure 1). The statistical results indicated that the effect size was too small to create significant differences between the two patient groups. Although the effect was too small to be meaningful, the up-and-down method is likely to allow for estimation of the ED₅₀ using a small sample size—for ethical reasons, clinicians must avoid providing inadequate analgesia to the greatest extent possible. Based on the estimated ED₅₀ of nefopam (62.1 mg), a randomized controlled study with a sufficient dose is recommended. Additionally, the greater ED₅₀ of nefopam in the present study may have been caused by remifentanyl-induced hyperalgesia. However, this is unlikely because

we induced general anesthesia using halogenated inhalational anesthetics and a continuous infusion of remifentanyl at low infusion rates rather than using nitrous oxide. Nonetheless, because we used a low dose of remifentanyl for continuous infusion during anesthesia, remifentanyl-induced hyperalgesia cannot be ruled out.^{28,29} Finally, we only observed patients until 30 minutes after the nefopam infusion was finished. A rescue analgesic was immediately administered to the patients who reported inadequate analgesia at this time. Considering the pharmacodynamic properties of nefopam, the onset of analgesia occurs at least 15 minutes after the beginning of infusion, and the peak analgesic effect is reached after 30 to 60 minutes.¹² For ethical reasons, we immediately used rescue analgesics 30 minutes after the end of infusion (<60 minutes after the start of infusion). These rescue analgesics may have masked the effects of nefopam in slow-response patients.

Conclusions

In conclusion, the ED₅₀ of nefopam for postoperative analgesia in patients who have undergone laparoscopic cholecystectomy is 62.1 mg (95% CI, 52.9–72.9 mg). We recommend that the nefopam dose is chosen after careful consideration of inter-individual variations and that injection pain is carefully monitored during nefopam administration. Although most adverse drug reactions are not serious, clinicians should be careful to observe all complications, including pain upon injection, when administering a higher dose of nefopam than previously recommended.

Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

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