Original Article

Korean J Health Promot 2024;24(2):56-66
pISSN: 2234-2141 • eISSN: 2093-5676
https://doi.org/10.15384/kjhp.2024.00052

Korean Journal of Health Promotion
KJHP

Effects of Intravenous Nefopam on Pain Relief in Patients with Acute Postoperative Pain: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Yehun JIN, MD[1,2], Seung-Kwon MYUNG, MD, PhD[2,3,4], Hangil KANG, MD[1], Woosik EOM, MD, PhD[1], Daehyun KIM, MD, PhD[1,2]

[1]Department of Anesthesiology and Pain Medicine, National Cancer Center, Goyang, Korea
[2]Department of Cancer AI & Digital Health, National Cancer Center Graduate School of Cancer Science and Policy, Goyang, Korea
[3]Cancer Epidemiology Branch, Division of Cancer Data Science, Research Institute, National Cancer Center, Goyang, Korea
[4]Department of Family Medicine and Center for Cancer Prevention and Detection, Hospital, National Cancer Center, Goyang, Korea

Abstract

Background: Although intravenous nefopam has been used for opioid-sparing strategy and pain relief, randomized controlled trials (RCTs) have shown inconsistent findings.
Methods: We searched core databases, PubMed, EMBASE, and the Cochrane library for RCTs on this research question in December 2022. Standardized mean difference (SMD) and weighted mean difference (WMD) were calculated using a random-effects meta-analysis.
Results: Of 708 studies identified from the databases, a total of 17 RCTs (n=1,173 patients) that met the inclusion criteria were included in the final meta-analysis. Overall, the consumption of cumulative opioid analgesics was significantly lower in the nefopam group than the control group, on arrival in the postanesthesia care unit (PACU) (SMD, −0.70; 95% confidence interval [CI], −1.01 to −0.39; I^2= 55.1%; n=7), at 24 hours (SMD, −0.65; 95% CI, −1.09 to −0.20; I^2=87.4%; n=9), and 48 hours (SMD, −0.82; 95% CI, −1.40 to −0.24; I^2=85.6%; n=6) after surgery. It also showed a significant lower pain score, on arrival in the PACU (WMD, −0.80; 95% CI, −1.27 to −0.32; I^2=69.6%; n=7) and 24 hours (WMD, −0.48; 95% CI, −0.79 to −0.16; I^2=0.0%, n=5). However, publication bias was observed (asymmetrical funnel plot and *P* for bias=0.005).
Conclusions: Intravenous nefopam showed an opioid-sparing effect and pain relief in the management of patients with acute postoperative pain.

Keywords: Nefopam, Pain, Randomized controlled trial, Meta-analysis

INTRODUCTION

Postoperative pain management is an important clinical challenge that could impact a patient's recovery and lead to complications. Although opioids are commonly used to prevent and treat postoperative pain, their use has been limited due to their common side effects such as dependence, sedation, and respiratory depression [1]. Opioids also can paradoxically cause

Received: April 18, 2024; **Revised:** June 20, 2024; **Accepted:** June 21, 2024
Corresponding author: Seung-Kwon MYUNG, MD, PhD
Department of Cancer AI & Digital Health, National Cancer Center Graduate School of Cancer Science and Policy, 323 Ilsan-ro, Ilsandong-gu, Goyang 10408, Korea
Tel: +82-31-920-0479 Fax: +82-31-920-2606 E-mail: msk@ncc.re.kr

increased pain, which is called opioid-induced hyperalgesia [2]. To address these concerns, healthcare providers are shifting away from opioids to a supplementation of non-opioid analgesics with multiple mechanisms of action [3,4]. By using these multi-analgesic approaches, patients can achieve optimal pain relief, while reducing the total amount of opioids needed and minimizing associated side effects [3,4]. Thus, postoperative pain management became to focus on opioid-sparing approaches that incorporate a variety of analgesic agents.

For decades, nefopam, which is a non-opioid, non-steroidal, centrally acting analgesic drug and was first introduced in France in the 1970s, has been used as an alternative and supplement to opioids [5], as well as for the purpose of controlling acute painful conditions such as postoperative pain, trauma, or cancer pain [6].

Previous randomized controlled trials (RCTs) have reported inconsistent findings regarding the effect of nefopam on reduction of opioid consumption and pain relief [7-23]. Several RCTs have shown its significantly beneficial effects [7,8,10-18,20,21], whereas other RCTs did not [9,19,22,23]. In 2008, a quantitative systematic review reported that there was limited evidence that nefopam might be a useful non-opioid analgesic in the management of postoperative pain [6]. However, it only included three RCTs, and since its publication, subsequent additional RCTs on this topic have been published.

Therefore, this study aimed to investigate the effect of intravenous (IV) nefopam for opioid-sparing strategy and pain relief in patients with acute postoperative pain using a meta-analysis of RCTs.

METHODS

This meta-analysis adhered to the criteria outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [24,25].

Search strategy

We searched core electronic databases, PubMed, EMBASE, and the Cochrane library for RCTs on this research question in December 5, 2022. Literature search was conducted without language restrictions, and the keywords were (Nefopam or Acupan). Article types were confined to 'RCTs and clinical trial'. We also reviewed the bibliographies of relevant articles to identify additional publications from previous review articles and reference lists.

Eligibility criteria

We included RCTs that fulfilled the following criteria: (1) Population, adult patients aged 18 years or older undergoing surgery under general anesthesia; (2) Intervention, perioperative administration of nefopam with opioid analgesics for postoperative pain control, IV administration via bolus injection, continuous infusion, or patient-controlled analgesia (PCA); (3) Comparisons, a placebo with opioid analgesics, or an equivalent amount of normal saline administered through the same route as the intervention group; (4) Outcome, cumulative opioid analgesics consumption and pain scores using a Numerical Rating Scale, a Visual Analogue Scale, or a Verbal Rating Scale.

Selection of studies

Two authors of this study independently reviewed and selected relevant studies based on the above mentioned selection criteria. Disagreements between the two authors were resolved by discussion. We included only full-text journal publications and excluded review articles, unpublished online clinical trial results, and abstracts. If studies overlapped, we selected the more comprehensive one. We also excluded studies that involved surgery under regional anesthesia.

Data extraction and quality assessment

In each study, we extracted the following items: author name, year of publication, number of study participants, type of surgery, type of anesthesia, nefopam regimen, postoperative analgesics, follow-up duration, and main findings.

The study quality for individual studies were assessed based on Cochrane risk of bias tool [26]. Those given a score higher than the average number of low risk of bias were considered as high-quality studies in this analysis.

Primary outcome measures

The primary outcome measures were cumulative opioid consumption on arrival in the postanesthesia care unit (PACU), at 12, 24, and 48 hours after operation, either intravenously or via IV PCA devices and resting pain scores at the same periods. Although some studies reported motion-dependent pain scores, we focused on the more commonly used resting pain scores. The secondary outcome measures included postoperative adverse events such as postoperative nausea and vomiting (PONV), confusion, sweating, tachycardia, dry mouth, dizziness, and sedation.

Statistical analysis

We calculated a pooled standardized mean difference (SMD) for cumulative opioid analgesic consumption and weighted mean difference (WMD) for pain scores with its corresponding 95% confidence intervals (CIs). When continuous results were reported as median and interquartile range (IQR), instead of mean±standard deviation, the median and IQR values were converted to the mean and standard deviation using Wan 2014 formula [27]. By incorporating effect sizes from multiple studies with different sample sizes and variances, we used a random-effects model meta-analysis based on the DerSimonian and Laird methods [26,28]. Study-wide heterogeneity was evaluated using Higgins I^2 to measure the overall variance [29]. An I^2 value of 50% or higher suggests that there may be substantial clinical, methodological heterogeneity [29]. Statistical analysis was performed using Stata/MP version 17.0 software package (StataCorp.).

RESULTS

Selection process

Fig. 1 shows a flow diagram for identifying relevant studies. A total of 708 articles were identified from three electronic databases and manual searches of relevant bibliographies. After removing 153 duplicates, the remaining 555 articles underwent an eligibility evaluation based on their titles and abstracts by two authors. Among them, 538 articles that did not meet the predefined selection criteria were excluded. A total of 17 articles were included in the final analysis [7-23].

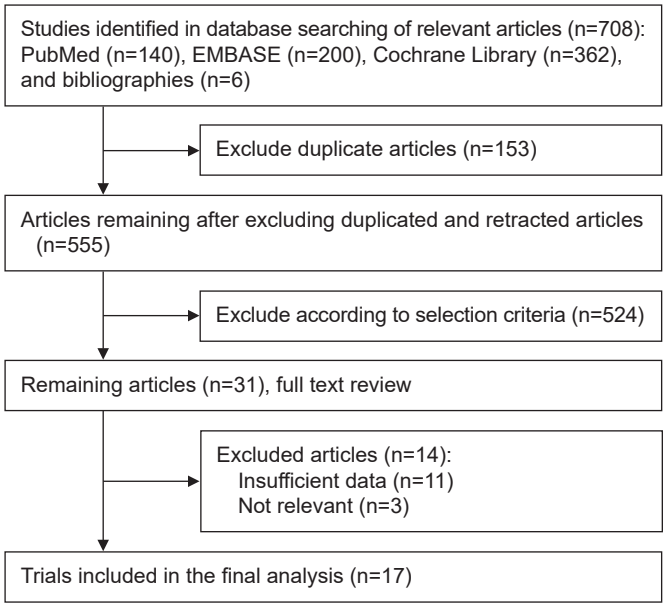

Fig. 1. Flow diagram for identification of relevant studies.

General characteristics of studies

Table 1 shows general characteristics of the included studies. The eligible studies were published between 2003 and 2022, with sample sizes ranging from 31 to 183. All study participants received general anesthesia. Methods of administration for nefopam varied from study to study. The assessment of pain scores was performed at between 5 minutes and 5 days after surgery across studies.

Quality assessment

As shown in Table 2, in the methodological quality score assessment based on the Cochrane risk of bias tool, nine studies showing a low risk of bias ≥ five domains among seven domains were classified as high-quality studies [10,12-14,16-18,20,23], while the remaining eight studies having a low risk of bias in less than five domains were classified as low-quality studies.

Publication bias was observed: the Begg's funnel plot was asymmetry, and P for bias from the Egger's test was 0.005 (Fig. 2).

Main findings

Consumption of cumulative opioid analgesics

Of 17 RCTs, 15 reported complete data on cumulative opioid consumption in the nefopam group compared to the control group. The cumulative opioid consumption was significantly lower in the nefopam group, on arrival in the PACU (SMD, −0.70; 95% CI, −1.01 to −0.39; I^2=55.1%, n=7), at 24 hours (SMD, −0.65; 95% CI, −1.09 to −0.20, I^2=87.4%, n=9), and 48 hours (SMD, −0.82; 95% CI, −1.40 to −0.24; I^2=85.6%, n=6) after surgery (Fig. 3). However, no significant difference was observed at 12 hours (SMD, −0.11; 95% CI, −0.40 to 0.17; I^2=16.2%, n=3).

Postoperative pain scores

In a meta-analysis of seven RCTs reporting complete data on pain scores, the nefopam group showed a lower pain scores than the control group, on arrival in the PACU (WMD, −0.80; 95% CI, −1.27 to −0.32; I^2=69.6%, n=7) and 24 hours (WMD, −0.48; 95% CI, −0.79 to −0.16; I^2=0.0%, n=5) (Fig. 4). The pain scores at 12 hours (WMD, −0.32; 95% CI, −1.00 to 0.35; I^2=73.8%, n=3) and 48 hours (WMD, −0.36; 95% CI, −1.06 to

https://doi.org/10.15384/kjhp.2024.00052

Table 1. Characteristics of randomized controlled trials included in the final meta-analysis (n=17)

No.	Source	No. of patient (E/C)	Type of surgery	Anesthesia	Nefopam regimen	Postoperative analgesic	Assessment of pain scores	Finding
1	Tramoni et al. [7] (2003)	31/31	Laparotomy	Thiopental, remifentanil, isoflurane	80 mg IV postoperatively, day^{-1} during 2 day, started in PACU	IV morphine PCA for 48 hr +propacetamol 2 g every 6 hr	10, 20, 30 min, 1, 2 hr in PACU, every 4 hr in ward	At 48 hr, cumulative-morphine consumption was 58±28 mg in the placebo group and 39±28 mg in the nefopam group (P<0.01).
2	Du Manoir et al. [8] (2003)	93/90	Hip arthroplasty	Thiopental or propofol, sufentanil, isoflurane, nitrous oxide	20 mg IV diluted in dextrose 5%, started at wound closure every 4 hr ended 24 hr	IV morphine PCA	PACU, 1, 4, 8, 12, 16, 20, 24 hr	PCA-administered morphine over 24 hr was significantly less for the nefopam group than the control group (21.2±15.3 and 27.3±19.2 mg, respectively, P=0.02).
3	Merle et al. [9] (2005)	20/20/20	Urologic laparotomy	Propofol, sufentanil, desflurane, nitrous oxide	20 mg bolus at the end of surgery+80 mg (Group 1) or 120 mg (Group 2) IV over 24 hr	IV morphine PCA	PACU, 12, 24, 36, 48 hr	In the placebo group, the median (IQR) morphine consumption reached 29 mg (13–53 mg), whereas in patients receiving 80 and 120 mg nefopam, it levelled to 44 mg (11–54 mg) and 35 mg (9–82 mg) (P>0.05).
4	Aveline et al. [10] (2009)	24/24/25	Total knee replacement	Propofol, remifentanil, sevoflurane, nitrous oxide	0.2 mg kg^{-1} over 20-min after anesthetic induction+120 μg kg^{-1} hr^{-1} 5 min until the end of surgery+60 μg kg^{-1} hr^{-1} until POD2	IV 0.15 mg/kg morphine 20 min before skin closure, IV morphine PCA for 48 hr+IV 3 mg morphine rescue	PACU, 2, 6, 12, 24, 48 hr	At 48 hr, cumulative morphine dose was higher in the placebo group than in nefopam group (72.1±8.7 mg vs. 52.2±7.5 mg, P<0.0001). When compared to placebo, patients in the nefopam groups had lower VAS scores at rest, only in the recovery and at 2 hr (P<0.0001 and P=0.003, respectively).
5	Park et al. [11] (2015)	33/33	Laparoscopic gastrectomy	Propofol, remifentanil	Mixed with IV PCA (nefopam 100 mg, fentanyl 30 μg/kg diluted in 100 mL N/S) started after 90 min from anesthesia induction	IV fentanyl PCA	30 min, 24 hr	Analgesic demand for 24 hr after PCA administration was 1.6±0.8 time in the control group, 1.1±0.6 time in the nefopam group (P < 0.05).
6	Kim et al. [12] (2015)	47/48	Renal transplantation	Propofol, remifentanil, desflurane	Continuous infusion of 160 mg diluted with 200 ml N/S at a rate of 4 mL/hr after reperfusion over 48 hr	IV fentanyl PCA, IV 50 μg fentanyl 10 min before the end of the operation	1, 6, 12, 24, 48 hr	Continuous IV administration of nefopam 160 mg for the first 48 hr after reperfusion of the graft kidney demonstrated 19% fentanyl-sparing effect with concomitant improvement of post-operative analgesia.
7	Choi et al. [13] (2016)	18/18/18	Laparoscopic cholecystectomy	Propofol, remifentanil, sevoflurane	0.3 mg/kg at the induction of anesthesia followed by a continuous infusion of 0.065 mg/kg/hr	IV morphine 20 mg in PACU for rescue	5, 15, 30, 45, 60 min	In control group, there were higher request of morphine in regard to the proportion (78% vs. 22%).
8	Jin et al. [14] (2016)	35/36	Laparotomy	Propofol, sevoflurane	Mixed with IV PCA (25 μg/mL fentanyl and 2.4 mg/mL nefopam) over 24 hr	IV fentanyl PCA	1, 2, 6, 12, 24 hr	PCA fentanyl consumption (496.4±287.0, 767.4±370.1) and total fentanyl consumption (533.5±288.0, 811.6±377.6) remained significantly lower in the nefopam group than the control group (P=0.005 and P=0.005, respectively).

(Continued to the next page)

Table 1. Continued

No.	Source	No. of patient (E/C)	Type of surgery	Anesthesia	Nefopam regimen	Postoperative analgesic	Assessment of pain scores	Finding
9	Li et al. [15] (2016)	16/15/17	Abdominal surgery	Fentanyl, thiopental, isoflurane, nitrous oxide, sufentanil	Continuous infusion of 3 mg/kg/hr in PACU	IV morphine PCA	0.5, 1, 2, 6, 12, 24 hr	The mean cumulative dose of morphine administered during the 24 hr period was 33.4±2.5 mg and 26.94±3.5 mg in the control and nefopam (P<0.05) groups. The VRS and VAS scores were significantly higher in the control group than in nefopam groups at 1, 2, 6, and 12 hr postoperatively.
10	Moon et al. [16] (2016)	28/27	Laparoscopic total hysterectomy	Thiopental, desflurane, nitrogen oxide	A single bolus of 10 mg fentanyl and 4 mg nefopam was injected at skin closure+fentanyl 2.5 mg/mL nefopam via PCA without continuous basal infusion	IV fentanyl PCA+30 mg of IV ketorolac rescue	1, 2, 6, 12, 24, 48 hr	Total fentanyl consumption at 48 hr was 236.1±12.81 mg in Group A (fentanyl 1,000 μg), 107.5±74.0 mg in Group B (fentanyl 500 μg+nefopam 200 mg), and 120.7±91.1 mg in Group C (fentanyl 500 μg+nefopam 400 mg) (P<0.001 for Group A vs. Group B and P<0.001).
11	Park et al. [17] (2016)	20/21	Bimaxillary osteotomy	Propofol, remifentanil, sevoflurane	20 mg with 50 mL of N/S 30 min before induction+24 hr IV infusion of 5 mg/10 mL/hr beginning postoperatively	IV fentanyl 50 μg in PACU, IM diclofenac sodium 75 mg in ward for rescue	0.5, 1, 6, 24 hr	In PACU, pain was significantly lower in the nefopam group than in the control (median [IQR] 4.6 [3.0–6.0] vs. 6.0 [5.5–7.0], P=0.002). On ward, the difference was statistically significant 6 and 24 hr postoperatively (P<0.005).
12	Na et al. [18] (2016)	41/42	Breast cancer surgery	Propofol, alfentanil, sevoflurane	20 mg IV preoperatively	IV fentanyl 0.5 μg/kg rescue in PACU, ketorolac, meloxicam	PACU, 6, 24 hr	The NRS of postoperative pain was significantly lower in the nefopam than in the control group in the PACU (4.5±2.2 vs. 5.7±1.5, P=0.01), at 6 hr (3.0±1.6 vs. 4.5±1.3, respectively, P<0.001), and at 24 hr (3.1±1.1 vs. 3.8±1.5, P=0.01).
13	Cuvillon et al. [19] (2017)	37/32	Abdominal surgery	Propofol, sufentanil, sevoflurane, nitrous oxide	5 mg/hr continuous IV infusion up to 120 mg, started at the end of the surgery until 48 hr	IV morphine PCA, IV 2 mg morphine rescue, IV paracetamol 1 g/6 hr	PACU, 6, 12, 24, 36, 48 hr	The cumulative morphine consumption in PACU to 48 hr was not different between the nefopam and control groups, with 53±37 mg and 54±34 mg (P=0.85).
14	Kim et al. [20] (2017)	20/20/20	Laparoscopic cholecystectomy	Propofol, remifentanil, sevoflurane	0.3 mg/kg during anesthesia induction+65 μg/kg/hr was infused continuously during surgery	IV fentanyl 50 μg+IV fentanyl 25 μg for follow-up dose rescue	1, 5, 15, 30, 45, 60 min	Nefopam group (36.3±37.6 μg, P=0.001) has less fentanyl requirements after surgery than control group (76.3±31.9 μg, P=0.042). They also had lower Vas scores than control group at the 1, 5, and 45 min time points in the PACU (P=0.001, 0.026, and <0.001).
15	Na et al. [21] (2018)	28/32	Laparoscopic gastrectomy	Propofol, remifentanil	20 mg diluted in 100 mL N/S after anesthesia induction and at the end of the operation	IV fentanyl PCA+tramadol (37.5 mg)/acetaminophen (325 mg) TID	PACU, 6, 24, 48, 72 hr, 5 day	Patients in the nefopam group required less fentanyl via IV PCA than did those in the control group during the first 6 hr (323.8±119.3 μg vs. 421.2±151.6 μg, P=0.009).

(Continued to the next page)

 https://doi.org/10.15384/kjhp.2024.00052

Table 1. Continued

No.	Source	No. of patient (E/C)	Type of surgery	Anesthesia	Nefopam regimen	Postoperative analgesic	Assessment of pain scores	Finding
16	Yeo et al. [22] (2022)	49/50	Video-assisted thoracoscopic surgery	Propofol, remifentanil, sevoflurane	20 mg diluted in 100 mL N/S after induction and 15 min before the end of surgery	IV fentanyl PCA, IV 0.01 mg/kg of hydromorphone and 1 g of acetaminophen 20 min before the end of surgery	PACU, 6, 12, 24, 72 hr	Intraoperative nefopam administration did not decrease total opioid consumption or postoperative pain intensity during the first 72 hr after VATS for lung cancer.
17	Chalermkitpanit et al. [23] (2022)	49/45	Minimally invasive spine surgery	Propofol, desflurane, fentanyl	20 mg diluted in 100 mL N/S intraoperatively, followed by continuous infusion of 80 mg of nefopam diluted in 500 mL of N/S postoperatively for 24 hr	1,000 mg of paracetamol orally every 6 hr+daily 90 mg of etoricoxib+daily 75 mg of pregabalin	PACU, 24, 48, 72 hr	The addition of 24-hr IV nefopam in a multimodal analgesic regimen provided no beneficial effects on morphine consumption, postoperative pain, or functional outcomes.

E/C, experiment/control group; IQR, interquartile range; IV, intravenous; NFP, nefopam; NRS, Numerical Rating Scale; N/S, normal saline; PACU, postanesthesia care unit; PCA, patient-controlled analgesia; POD, postoperative day; VAS, Visual Analogue Scale; VRS, Verbal Rating Scale.

Table 2. Summary of risk of bias assessment for randomized controlled trials based on the Cochrane risk of bias tool

Source	Random sequence generation	Allocation concealment	Blinding of participants, and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	No. of low risk of bias
Tramoni et al. [7] (2003)	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	2
Du Manoir et al. [8] (2003)	Unclear	Unclear	Low	Unclear	Low	Low	Unclear	3
Merle et al. [9] (2005)	Unclear	Unclear	High	Unclear	Low	Low	Unclear	2
Aveline et al. [10] (2009)	Low	Low	Low	Low	Low	Unclear	Unclear	5
Park et al. [11] (2015)	Unclear	Unclear	High	High	Low	Low	Unclear	2
Kim et al. [12] (2015)	Low	Low	Low	Low	Low	Low	Unclear	6
Choi et al. [13] (2016)	Low	Low	Low	Low	Low	Low	Unclear	6
Jin et al. [14] (2016)	Low	Unclear	Low	Low	Low	Low	Unclear	5
Li et al. [15] (2016)	Low	High	High	Low	Low	Unclear	Unclear	3
Moon et al. [16] (2016)	Low	High	Low	Low	Low	Low	Unclear	5
Park et al. [17] (2016)	Low	Low	Low	Low	Low	Low	Unclear	6
Na et al. [18] (2016)	Low	High	Low	Low	Low	Low	Unclear	5
Cuvillon et al. [19] (2017)	Low	High	Low	Low	High	Low	Unclear	4
Kim et al. [20] (2017)	Low	High	Low	Low	Low	Low	Unclear	5
Na et al. [21] (2018)	Low	High	Low	High	Low	Low	Unclear	4
Yeo et al. [22] (2022)	Low	Low	High	High	Low	Low	Unclear	4
Chalermkitpanit et al. [23] (2022)	Low	Low	Low	High	Low	Low	Unclear	5

0.33; I^2=0.0%, n=3) showed no statistical differences between the two groups.

Adverse events

Table 3 shows the differences of adverse events between the nefopam and placebo groups. Dry mouth, PONV, and dizziness were frequently observed in both groups with the prevalence range of about 31%-76%. There was no significant difference in PONV, confusion, tachycardia, and dizziness between the two groups. However, sweating (RR, 2.29; 95% CI, 1.14 to 4.61) and dry mouth (RR, 1.32; 95% CI, 1.10 to 1.58) were significantly higher in the nefopam group compared to the placebo group.

DISCUSSION

In this meta-analysis, perioperative nefopam administration showed a significantly lower cumulative opioid consumption and pain score than that in the control group. The use of nefo-

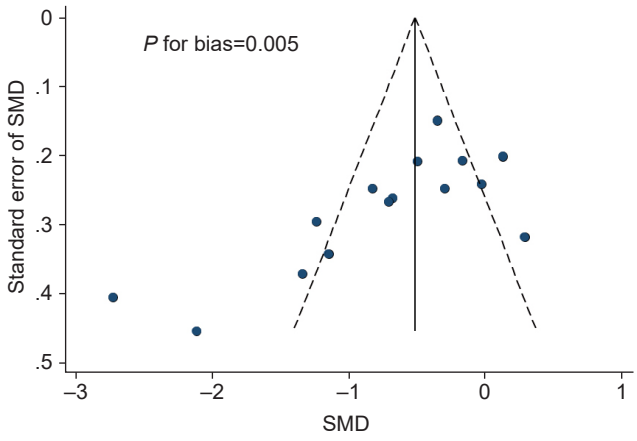

Fig. 2. Funnel plot for identifying publication bias in a meta-analysis of randomized controlled trial on the cumulative opioid consumption between the nefopam and control groups. SMD, standardized mean difference.

pam was generally safe and showed no serious adverse event: it showed higher frequency of tachycardia, sweating, and dry mouth; no significant difference in frequency of PONV and confusion was observed.

Nefopam is a non-opioid analgesic that acts centrally on the nervous system to reduce pain perception. The exact mechanism of action of nefopam has not been fully understood. However, it is known to involve multiple mechanisms. First, nefopam modulates descending pain pathways by inhibiting reuptake of triple neurotransmitters, such as norepinephrine, serotonin, or dopamine [30]. By inhibiting the reuptake of these neurotransmitters, nefopam increases their concentration in the synapses between nerve cells, which can lead to an enhancement of the descending inhibitory pain pathways. Second, by influencing the activity of voltage-gated ion channels, nefopam can affect the excitability of neurons and reduce the transmission of pain signals. Moreover, nefopam has been found to modulate glutamate transport and inhibits the activity of N-methyl-D-aspartate receptors, resulting in antihyperalgesic

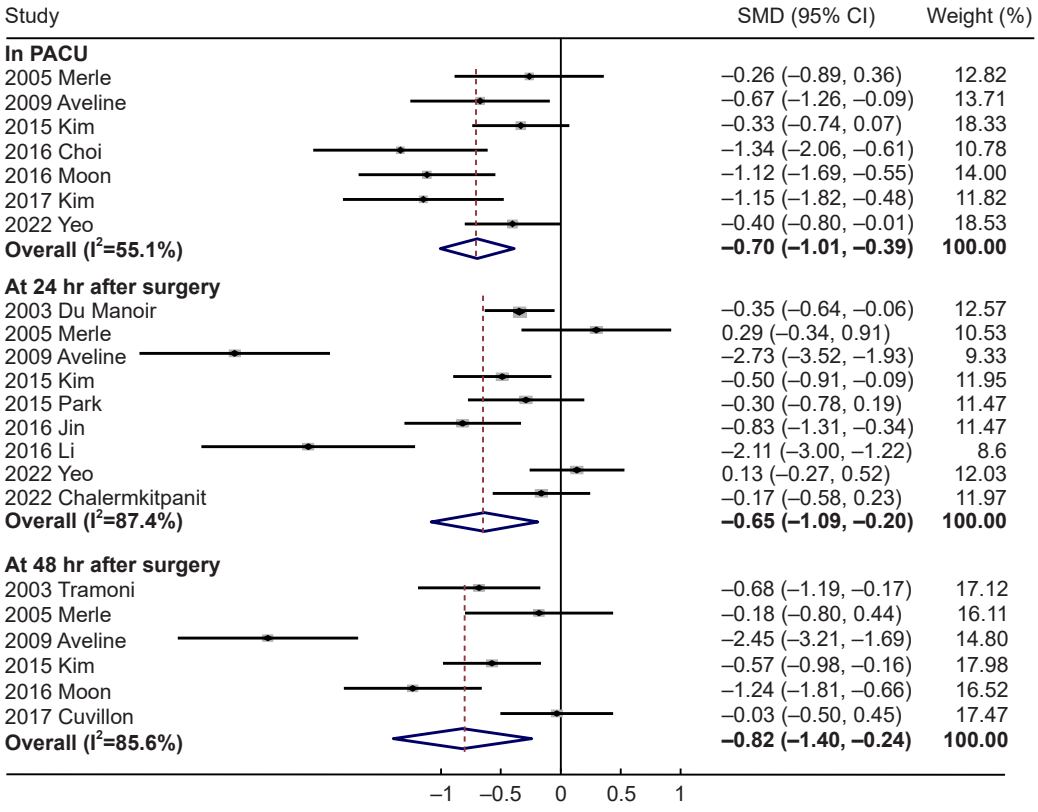

Fig. 3. Perioperative nefopam administration and cumulative opioid consumption in a meta-analysis of randomized controlled trials in the PACU, at 24 hours, and 48 hours after surgery. CI, confidence interval; PACU, postanesthesia care unit; SMD, standardized mean difference.

https://doi.org/10.15384/kjhp.2024.00052

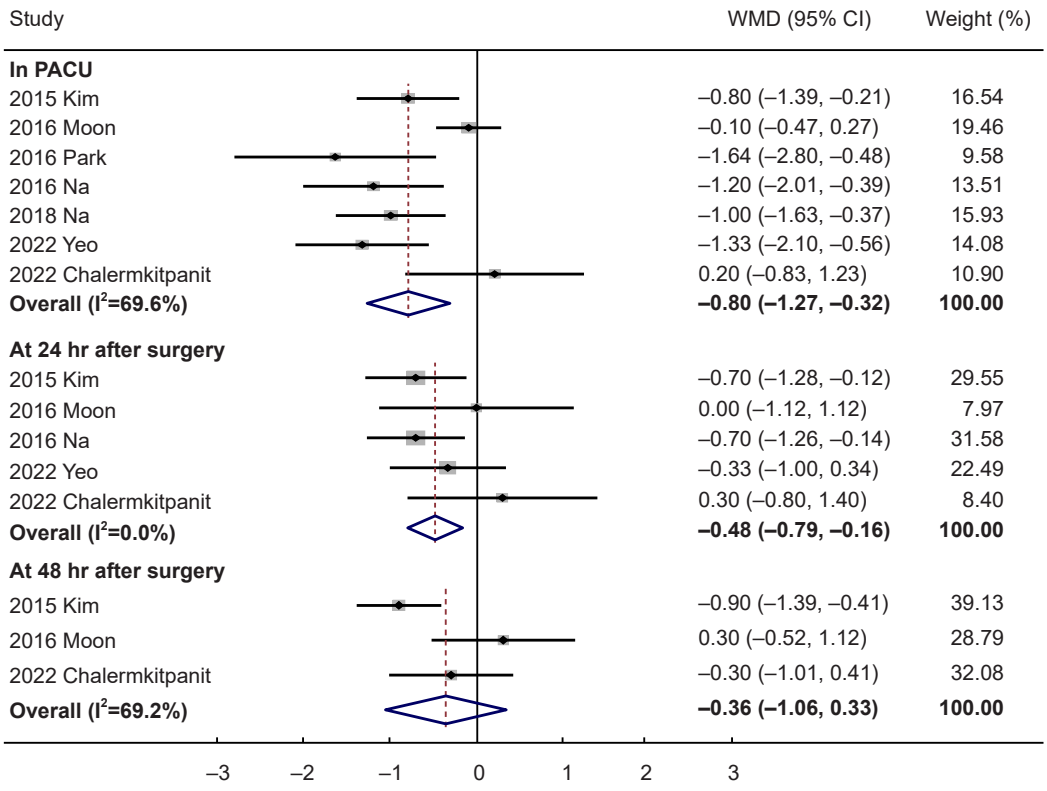

Fig. 4. Perioperative nefopam administration and pain score in a meta-analysis of randomized controlled trials in the PACU, at 24 hours, and 48 hours after surgery. CI, confidence interval; PACU, postanesthesia care unit; WMD, weighted mean difference.

Table 3. Differences of adverse events between the nefopam and placebo groups

Adverse event	No. of study	Prevalence of adverse events (%)		RR (95% CI)	Heterogeneity I^2 (%)
		Nefopam	Placebo		
PONV	10	31.3	35.4	0.94 (0.78–1.13)	0.0
Confusion	4	8.15	11.5	0.68 (0.32–1.48)	100
Sweating	8	8.9	3.2	2.29 (1.14–4.61)	0.0
Tachycardia	3	3.2	1.1	2.17 (0.57–8.27)	0.0
Dry mouth	3	75.9	59.0	1.32 (1.10–1.58)	0.0
Dizziness	4	33.3	31.3	1.05 (0.69–1.61)	42.8

CI, confidence interval; PONV, postoperative nausea and vomiting; RR, relative risk.

effects [31,32]. Finally, it has been shown to inhibit other neurotransmitters involved in pain processing, such as substance P, calcitonin gene-related peptide, and neurokinin A, which neurotransmitters are known to induce neuropathic pain by vasodilation and plasma protein extravasation [33-35]. The action of nefopam on the glutaminergic pathway has already been proven in in vitro studies, and its antiallodynic and antinociceptive effects on neuropathic pain have also been demonstrated in in vivo animal studies [35].

This meta-analysis provides a significant advantage over a previous review by including a larger number of articles and a larger sample size. Previous studies have yielded only limited evidence on the efficacy of nefopam as a non-opioid analgesic in surgical patients. However, this meta-analysis provides a high level of evidence supporting its effectiveness by pooling data from all the available studies, increasing statistical power and precision.

We adopted a uniform route of administration, specifically IV administration of nefopam, while previous reviews did not differentiate between different routes of administration [6].

The current meta-analysis showed substantial heterogeneity regarding the cumulative opioid consumption and pain score by the use of IV nefopam. It is related with a variation in dosages across individual studies. A median effective dose (ED50) of nefopam for moderate surgical pain is estimated 21.7-28 mg [36,37]. The dosage of nefopam used in studies ranged from 20 to 160 mg. Several studies reported that the estimated ED50 of nefopam as a sole agent is about 60 mg in postoperative patients who have undergone laparoscopic cholecystectomy, which dosage is higher than those commonly recommended [38]. Thus, some dosages used in the studies included in our analysis might be insufficient to effectively treat acute postoperative pain, given the varying degrees of pain associated with different types of surgeries. Substantial heterogeneity is also due to a diversity of surgical procedures, which can result in varying degrees of pain. If the pain at the time of surgery is not severe, the effect of postoperative analgesics might be underestimated. For example, laparoscopic surgery typically causes less pain than open abdominal surgery. Thus, the difference in pain scores between the nefopam and control groups might be minimal, and it might lead to a minimal difference in the dosage of opioid analgesics between groups.

In the meantime, although PONV have previously been known to be major adverse effects of perioperative administration of nefopam, our study showed no significant difference in the incidence of PONV between the two groups. Sweating was higher in the nefopam group than the control group, which is consistent with the finding of the previous systematic review [6]. Our study also found a higher incidence of dry mouth in the nefopam group compared to the control group, which contradicts the previous review [6].

Our meta-analysis has several limitations. First, as described earlier, there was substantial heterogeneity in findings, which are mainly due to clinical heterogeneity. That is, there were substantial differences in underlying diseases in the study participants, dosages and timing of nefopam, and time for pain assessment and opioid consumption. Second, most studies reported pain scores limited to the resting state, although the evaluation of dynamic pain for postoperative recovery is also important. Last, our meta-analysis showed publication bias. Thus, the effect of nefopam might be overestimated.

In conclusion, the current meta-analysis of RCTs found that over all, the use of the IV nefopam showed an opioid-sparing effect and pain relief in the management of patients with acute postoperative pain.

ORCID

Yehun JIN, https://orcid.org/0000-0001-6636-1245
Seung-Kwon MYUNG, https://orcid.org/0000-0001-8911-1345
Hangil KANG, https://orcid.org/0009-0006-6583-5596
Woosik EOM, https://orcid.org/0000-0003-1524-0325
Daehyun KIM, https://orcid.org/0000-0002-4144-1182

AUTHOR CONTRIBUTIONS

Dr. Seung-Kwon MYUNG had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors reviewed this manuscript and agreed to individual contributions.

Conceptualization: YJ and SKM. Methodology: YJ and SKM. Software: YJ and SKM. Validation: SKM. Formal analysis: YJ and SKM. Investigation: YJ, WE, and DK. Data curation: YJ and SKM. Writing-original draft: YJ and SKM. Writing-review & editing: all authors.

CONFLICTS OF INTEREST

No existing or potential conflict of interest relevant to this article was reported.

FUNDING

None.

DATA AVAILABILITY

The data presented in this study are available upon reasonable request from the corresponding author.

REFERENCES

1. Ballantyne JC, LaForge SK. Opioid dependence and addiction during opioid treatment of chronic pain. Pain 2007;129(3):235-55.
2. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. Pain Physician 2011;14(2):145-61.
3. Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg 1993;77(5):1048-56.
4. White PF. Multimodal analgesia: its role in preventing postoper-

ative pain. Curr Opin Investig Drugs 2008;9(1):76-82.
5. Girard P, Chauvin M, Verleye M. Nefopam analgesia and its role in multimodal analgesia: a review of preclinical and clinical studies. Clin Exp Pharmacol Physiol 2016;43(1):3-12.
6. Evans MS, Lysakowski C, Tramèr MR. Nefopam for the prevention of postoperative pain: quantitative systematic review. Br J Anaesth 2008;101(5):610-7.
7. Tramoni G, Viale JP, Cazals C, Bhageerutty K. Morphine-sparing effect of nefopam by continuous intravenous injection after abdominal surgery by laparotomy. Eur J Anaesthesiol 2003;20:990-2.
8. Du Manoir B, Aubrun F, Langlois M, Le Guern ME, Alquier C, Chauvin M, et al. Randomized prospective study of the analgesic effect of nefopam after orthopaedic surgery. Br J Anaesth 2003;91(6):836-41.
9. Merle JC, Vandroux D, Odin I, Dupuis JL, Bougault A, Mehaddi Y, et al. Effets analgésiques de l'administration intraveineuse continue de néfopam après chirurgie urologique [Analgesic effect of continuous intravenous nefopam after urological surgery]. Ann Fr Anesth Reanim 2005;24(1):13-8. French.
10. Aveline C, Gautier JF, Vautier P, Cognet F, Hetet HL, Attali JY, et al. Postoperative analgesia and early rehabilitation after total knee replacement: a comparison of continuous low-dose intravenous ketamine versus nefopam. Eur J Pain 2009;13(6):613-9.
11. Park JH, Kim DY, Park SY, Choi SR, Lee SC, Lee JH. Effect of nefopam for patient-controlled analgesia after laparoscopic gastrectomy. Anesth Pain Med 2015;10(3):175-9.
12. Kim SY, Huh KH, Roh YH, Oh YJ, Park J, Choi YS. Nefopam as an adjunct to intravenous patient-controlled analgesia after renal transplantation: a randomised trial. Acta Anaesthesiol Scand 2015;59(8):1068-75.
13. Choi SK, Yoon MH, Choi JI, Kim WM, Heo BH, Park KS, et al. Comparison of effects of intraoperative nefopam and ketamine infusion on managing postoperative pain after laparoscopic cholecystectomy administered remifentanil. Korean J Anesthesiol 2016;69(5):480-6.
14. Jin HS, Kim YC, Yoo Y, Lee C, Cho CW, Kim WJ. Opioid sparing effect and safety of nefopam in patient controlled analgesia after laparotomy: a randomized, double blind study. J Int Med Res 2016;44(4):844-54.
15. Li M, Li L, Xu YT, Wang X. Intravenous analgesics for pain management in postoperative patients: a comparative study of their efficacy and adverse effects. Trop J Pharm Res 2016;15(8):1799-806.
16. Moon JY, Choi SS, Lee SY, Lee MK, Kim JE, Lee JE, et al. The effect of nefopam on postoperative fentanyl consumption: a randomized, double-blind Study. Korean J Pain 2016;29(2):110-8.
17. Park HJ, Park JU, Yoo W, Moon YE. Analgesic effects of nefopam in patients undergoing bimaxillary osteotomy: a double-blind, randomized, placebo-controlled study. J Craniomaxillofac Surg 2016;44(2):210-4.
18. Na HS, Oh AY, Koo BW, Lim DJ, Ryu JH, Han JW. Preventive analgesic efficacy of nefopam in acute and chronic pain after breast cancer surgery: a prospective, double-blind, and randomized trial. Medicine (Baltimore) 2016;95(20):e3705.
19. Cuvillon P, Zoric L, Demattei C, Alonso S, Casano F, L'hermite J, et al. Opioid-sparing effect of nefopam in combination with paracetamol after major abdominal surgery: a randomized double-blind study. Minerva Anestesiol 2017;83(9):914-20.
20. Kim EM, Jeon JH, Chung MH, Choi EM, Baek SH, Jeon PH, et al. The effect of nefopam infusion during laparascopic cholecystectomy on postoperative pain. Int J Med Sci 2017;14(6):570-7.
21. Na HS, Oh AY, Ryu JH, Koo BW, Nam SW, Jo J, et al. Intraoperative nefopam reduces acute postoperative pain after laparoscopic gastrectomy: a prospective, randomized study. J Gastrointest Surg 2018;22(5):771-7.
22. Yeo H, Choi JW, Lee S, Sim WS, Park SJ, Jeong H, et al. The lack of analgesic efficacy of nefopam after video-assisted thoracoscopic surgery for lung cancer: a randomized, single-blinded, controlled trial. J Clin Med 2022;11(16):4849.
23. Chalermkitpanit P, Limthongkul W, Yingsakmongkol W, Thepsoparn M, Pannangpetch P, Tangchitcharoen N, et al. Analgesic effect of intravenous nefopam for postoperative pain in minimally invasive spine surgery: a randomized prospective study. Asian Spine J 2022;16(5):651-7.
24. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 2009;62(10):e1-34.
25. Moher D, Liberati A, Tetzlaff J, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Open Med 2009;3(3):e123-30.
26. Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JA. Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. Cochrane handbook for systematic reviews of interventions. 2nd ed. John Wiley & Sons; 2019. p. 205-28.
27. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14:135.

28. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7(3):177-88.
29. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21(11):1539-58.
30. Piercey MF, Schroeder LA. Spinal and Supraspinal sites for morphine and nefopam analgesia in the mouse. Eur J Pharmacol 1981;74(2-3):135-40.
31. Verleye M, André N, Heulard I, Gillardin JM. Nefopam blocks voltage-sensitive sodium channels and modulates glutamatergic transmission in rodents. Brain Res 2004;1013(2):249-55.
32. Novelli A, Díaz-Trelles R, Groppetti A, Fernández-Sánchez MT. Nefopam inhibits calcium influx, cGMP formation, and NMDA receptor-dependent neurotoxicity following activation of voltage sensitive calcium channels. Amino Acids 2005;28(2):183-91.
33. Lee JY, Sim WS, Cho NR, Kim BW, Moon JY, Park HJ. The antiallodynic effect of nefopam on vincristine-induced neuropathy in mice. J Pain Res 2020;13:323-9.
34. Verleye M, Gillardin JM. Contribution of transient receptor potential vanilloid subtype 1 to the analgesic and antihyperalgesic activity of nefopam in rodents. Pharmacology 2009;83(2):116-21.
35. Kim KH, Abdi S. Rediscovery of nefopam for the treatment of neuropathic pain. Korean J Pain 2014;27(2):103-11.
36. Delage N, Maaliki H, Beloeil H, Benhamou D, Mazoit JX. Median effective dose (ED50) of nefopam and ketoprofen in postoperative patients: a study of interaction using sequential analysis and isobolographic analysis. Anesthesiology 2005;102(6):1211-6.
37. Van Elstraete AC, Sitbon P. Median effective dose (ED50) of paracetamol and nefopam for postoperative pain: isobolographic analysis of their antinociceptive interaction. Minerva Anestesiol 2013;79(3):232-9.
38. Kim H, Lee DK, Lee MK, Lee M. Median effective dose of nefopam to treat postoperative pain in patients who have undergone laparoscopic cholecystectomy. J Int Med Res 2018;46(9):3684-91.

 https://doi.org/10.15384/kjhp.2024.00052