Journal of Applied Pharmaceutical Science Vol. 15(05), pp 024-039, May, 2025
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2025.203223
ISSN 2231-3354

Efficacy of nefopam in postoperative pain management: A systematic review of opioid consumption

Nagla Abdelmonim Bader[1], Mohammad M. Al-Ahmad[1*], Waiel Al Naeem[2], Mohammed Gamal Amer[3]

[1]Department of Clinical Pharmacy, College of Pharmacy, Al Ain University, Al Ain, United Arab Emirates.
[2]Clinical Pharmacy Department, Sheikh Khalifa Medical City, Abu Dhabi, United Arab Emirates.
[3]Clinical Pharmacy Department, Cairo University Hospitals, Cairo, Egypt.

ARTICLE HISTORY

Received on: 27/09/2024
Accepted on: 17/02/2025
Available Online: 05/04/2025

***Key words*:**
Nefopam, postoperative pain, management, opioids, opioid consumption, analgesia.

ABSTRACT

Previous research assessing the role of nefopam in postoperative pain management has yielded mixed results, with more evidence supporting a beneficial effect. This systematic review examines the efficacy of nefopam in reducing opioid consumption in postoperative patients and includes patient satisfaction measures and the frequency of adverse events. A comprehensive search strategy was performed in the following databases: PubMed, Web of Science, and Cochrane Library. Search terms used included "postoperative pain management" AND "nefopam", "nefopam" AND "opioid consumption", and "nefopam" AND "analgesia" OR "postoperative pain management". Studies involving postoperative adult patients receiving nefopam and compared with a control group were included. A risk of bias assessment was performed using the Cochrane ROB-2 tool. 17 articles passed the inclusion criteria. Findings indicated that nefopam significantly reduces opioid consumption in postoperative patients by an average of 38%. The overall analgesic effect of nefopam was superior to that of opioids alone, with a good margin of safety and a high degree of satisfaction in most patients. Nausea, sweating, and postoperative tachycardia were common in the treatment groups. From the findings, the study concludes that nefopam is an effective adjunctive postoperative analgesic that has a significant positive impact on pain management and reduction of opioid consumption. The study was registered on PROSPERO (ID: CRD42022364446).

INTRODUCTION

Postoperative pain management is crucial for promoting recovery, reducing the risk of complications, decreasing discomfort, and increasing patient satisfaction [1]. There are several approaches primarily aimed at achieving optimal analgesia while reducing the incidence of adverse events. These include the use of various adjunctive therapies such as nefopam, acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and ketamine, which aim to achieve adequate analgesia, minimize side effects and complications, and improve overall patient recovery [2,3]. Although opioids are the most used postoperative analgesics, they increase the risk of persistent postoperative pain [3] and the occurrence of adverse effects [4–7].

One of the approaches to achieve balanced analgesia is the use of nefopam alone or in combination with other opioids. Nefopam is a drug of choice for the management of moderate pain, especially postoperative pain and pain resulting from nerve damage [8]. It is a benzoxazocine synthesized from O-Benzoylbenzoic acid and has unique pharmacologic properties unlike other analgesics [9]. Additionally, nefopam is chemically distinct and pharmacologically unrelated to currently known analgesics. It does not affect platelet function and shows no anti-inflammatory effect when administered to patients [10–12].

Previous studies, including Girard *et al.* [8], Martinez *et al.* [13], Barazanchi *et al.* [14], Evans *et al.* [5],

*Corresponding Author
Mohammad M. Al-Ahmad, Department of Clinical Pharmacy, College of Pharmacy, Al Ain University, Al Ain, United Arab Emirates.
E-mails: mmajed01@hotmail.com, mohammad.alahmad @ aau.ac.ae

and Zhao *et al*. [15] examined the effects of nefopam on opioid administration in postoperative patients [5,8,13–15]. Girard *et al*. [8] reviewed 10 studies that investigated the role of nefopam in multimodal analgesia. The results in 8 of the 10 studies indicated that the combination of nefopam with other opioid analgesics resulted in pain reduction in patients [8]. Martinez *et al*. [13] evaluated the analgesic efficacy and safety of nefopam for postoperative pain relief. They found that nefopam provided analgesia and was non-inferior to other analgesics, including opioids [13]. In another systematic review, Barazanchi *et al*. [14] also concluded that the administration of nefopam, together with paracetamol, provided effective pain relief in postoperative patients [14].

Evans *et al*. [5] conducted a meta-analysis of the efficacy and safety of nefopam compared with other analgesics in the management of postoperative pain. The study showed that nefopam was as effective as other analgesics, including opioids and NSAIDs, in controlling postoperative pain. However, several side effects were also mentioned [5]. The study also indicated that nefopam was associated with an increased risk of adverse events such as nausea, vomiting, and sweating [5]. Finally, Zhao *et al*. [15] examined the safety and efficacy of nefopam for pain management in laparoscopic cholecystectomy in a meta-analysis. Significant differences were found between the treatment (nefopam) and placebo groups, with the former showing lower pain scores and adverse effects compared to the latter [15].

Although previous reviews have indicated the pain-reducing effect of nefopam, there is no quantitative measure of opioid reduction in postoperative patients. Additionally, there is still an unclear explanation of the association between nefopam use and reduction in opioid consumption and the incidence of adverse events in postoperative patients. Therefore, this study builds on the limitations of previous studies and attempts to fill the existing gap by providing a comprehensive summary of the available literature on the potential role of nefopam in reducing opioid consumption for pain management in postoperative patients. It also examines the level of patient satisfaction with nefopam treatment and the potential occurrence of adverse events during postoperative use.

METHODS

The MEDLINE®, EMBASE, Google Scholar, and Cochrane Library databases were searched for studies that had evaluated the efficacy and safety of nefopam in relation to opioid consumption in postoperative patients. Open web sources were also searched. Database searches were conducted between January 2023 and March 2023.

Inclusion criteria

Studies involving postoperative adult patients who had been given nefopam and compared with a control group were included for review. Only studies published in peer-reviewed journals were integrated. The review also used studies published between 2000 and 2023 since nefopam use has increased in the last two decades.

Exclusion criteria

Studies that either did not involve postoperative adult patients or had not been published in peer-reviewed journals were excluded from the current review. Additionally, studies involving animals and those that did not compare nefopam to a control group were excluded.

Search strategy

A literature search was conducted using precise keywords based on a Problem/Patient, Intervention, Comparative, and Results technique, as well as topic titles and Boolean Operators. The phrases "opioid," "postoperative," and "nefopam" were used as keywords. Search terms used included postoperative pain management, nefopam, analgesia, and opioid consumption.

1. Impact: ("impact" OR "impactful" OR "impacting" OR "impacts" OR "impacted") [All Fields] OR "impacted" [MeSH Terms].

2. Nefopam: "nefopam" [MeSH Terms] OR "nefopam" [All Fields].

3. Opioid: ("analgesics, opioid" [Pharmacological Action] OR "analgesics, opioid" [MeSH Terms] OR ("analgesics" [All Fields] AND "opioid" [All Fields]) OR "opioid analgesics" [All Fields] OR "opioid" [All Fields] OR "opioids" [All Fields] OR "opioid's" [All Fields]).

4. Consumption: "consumptions" [All Fields] OR "economics" [MeSH Terms] OR "economics" [All Fields] OR "consumption" [All Fields].

5. Postoperative: "postoperative period" [MeSH Terms] OR ("postoperative" [All Fields] AND "period" [All Fields]) OR "postoperative period" [All Fields] OR "postop" [All Fields] OR "postoperative" [All Fields] OR "postoperatively" [All Fields] OR "postoperatives" [All Fields].

6. Patients: ("patient's" [All Fields] OR "patients" [MeSH Terms] OR "patients" [All Fields] OR "patient" [All Fields] OR "patients'" [All Fields]).

Based on the research topic and search strategy, a PICOS question was formulated as follows: Population: patients undergoing postoperative treatment.

Intervention: administration of nefopam.

Comparison: use of opioid analgesics.

Outcome: impact on patients' consumption and occurrence of adverse effects.

PICOS question: In adult postoperative patients, does nefopam administration result in a significant reduction in opioid consumption and occurrence of adverse effects compared to opioid analgesics without nefopam?

After screening and selection of studies for systematic review, a risk of bias (ROB) assessment was performed using the Cochrane ROB-2 tool. ROB-2 is a recently updated tool that researchers can use to assess articles against six main criteria [16].

DistillerSR was used for data extraction and subsequent visualization using descriptive statistics. This software streamlines the collection, screening, and analysis of literature using automation techniques [17]. A standardized data extraction form was used by three reviewers to extract

and review the data. Each reviewer assessed all the studies and extracted data using the template, followed by a joint critical evaluation to harmonize potential discrepancies [18]. Through discussion and consensus, emerging discrepancies were addressed and solved.

The most important information from the studies in question was extracted in a separate table. The following information was requested during data extraction: author and year of publication; information on the participants—age, gender, duration of the postoperative phase; response rate; study groups and interventions; study duration; study country; type of publication (Table 1).

Finally, the results were summarized in another separate table. The information obtained from the eligible studies included the following: Study groups and interventions, indicators of postoperative pain, indicators of opioid consumption, impact on opioid consumption, the percentage reduction in opioid consumption, patient satisfaction with treatment, safety, and incidence of adverse events (Table 3).

PROSPERO REGISTRATION

This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42022364446. Details of the protocol can be accessed at: https://www.crd.york.ac.uk/prospero/.

RESULTS

Characteristics and summary of the eligible studies

The study selection process was conducted under strict adherence to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. A total of 454 studies were identified through initial database searches, with another four identified from web sources. Eight studies were removed as duplicates, with the remaining 450 studies screened. 401 studies that did not meet the inclusion criteria were excluded upon screening. Only 49 studies were evaluated for eligibility, with 32 being excluded for overlapping data and involvement of adults without postoperative pain. The remaining 17 studies were included for analysis. Figure 1 shows the PRISMA flow diagram of the systematic review strategy.

The low number of eligible studies (n = 17) reflects the stringent inclusion criteria applied to ensure the selection of high-quality and relevant data. Several studies were excluded due to limited methodological rigor, small sample sizes, or non-alignment with the research objective. This careful selection was essential to ensure robust findings and minimize bias, despite the limited pool of suitable studies.

Most studies (n = 4) were conducted in South Korea, whereas others were conducted in the United States (n = 3), the Republic of Korea (n = 3), Thailand (n = 3), and France [2]. Two studies were wider than one country. The remaining two studies were designated as "global" because they were conducted in different regions. A total of 2,617 adults were included in 16 studies. However, in one of the systematic reviews, the exact number of participants in the integrated studies was not provided [8]. All participants underwent postoperative pain management. Table 1 lists all study characteristics of the included articles.

Mimoz *et al.* [6] found that pain relief and reduced opioid consumption were higher when nefopam was administered together with other analgesics, especially paracetamol. Adverse effects such as nausea and dizziness also occurred [6]. du Manoir *et al.* [4] found that significantly less morphine was administered via patient-controlled analgesia (PCA) in the nefopam group [4]. On the other hand, Kapfer *et al.* [19] concluded that tachycardia and excessive sweating were more common in patients receiving nefopam than in the other two groups (isotonic saline and ketamine). Pain relief was faster in the nefopam and ketamine groups than in the control group after the additional morphine infusion was initiated [19]. Evans *et al.* [5] showed that opioid consumption and pain intensity decreased significantly in the nefopam group [5].

Richebé *et al.* [20] found significant changes in opioid consumption between the treatment and control groups. No adverse effects were reported [20]. Kim and Abdi [10] found a significant decrease in opioid consumption in the treatment groups receiving either nefopam alone or nefopam and fentanyl. Choi *et al.* [1] also showed that concomitant administration of nefopam or ketamine significantly decreased consumption of remifentanil and morphine [1]. Girard *et al.* [8] showed lower morphine consumption, with no adverse effects reported in the nefopam group [8]. Moon *et al.* [21] found no difference in satisfaction between patients receiving fentanyl and those receiving fentanyl with nefopam [21].

Son *et al.* [22] reported side effects such as postoperative nausea and vomiting [22]. Likewise, Zhao *et al.* [15] reported opioid-related side effects such as nausea, vomiting, and pruritus [15]. According to Nair [23] and Na *et al.* [24], there was lower opioid consumption and lower levels of chronic pain after nefopam use [23,24]. Pasutharnchat *et al.* [25] reported that patients in the nefopam group experienced significant pain reduction. Adverse events such as dizziness, drowsiness, sweating, dry mouth, and nausea occurred in both groups [25]. In a separate study, Lekprasert *et al.* [26] found that the nefopam group had similar postoperative pain scores compared to the control group [26]. According to Jung *et al.* [12], there was no statistically significant difference in numeric rating scale (NRS) scores between groups throughout the postoperative period [12].

Chalermkitpanit *et al.* [27] showed that there was no significant difference in morphine consumption between the nefopam group and the control group. There was also no significant difference in postoperative pain scores between the two groups. However, morphine consumption was slightly lower in the nefopam group [27]. On the other hand, Yoon *et al.* [28] found that the nefopam group had significantly lower fentanyl consumption compared with the control group. The nefopam group also had a significantly lower pain score. However, there were no significant differences in the occurrence of side effects, quality of recovery, and length of hospital stay [28].

Table 1. Data extraction summary for included studies.

Article number	Author & publication year	Participants (Age, gender, duration of postoperative period)	Response ratio (Number of respondents)	Study groups and interventions s	Study duration	Study country	Publication type
Article 1	Mimoz *et al.* [6]	120 participants, male and female, aged between 18 and 75 years.	93% (112 out of 120 participants were studied)	Group 1 (Control group)—PCA morphine alone. Group 2 (Nefopam group)—PCA morphine + nefopam 20 mg after every 4 hours. Group 3 (Propacetamol group)—PCA morphine + propacetamol 2 g every 6 hours.	10 months	France	Randomized controlled study.
Article 2	du Manoir *et al.* [4]	201 participants, male and female, aged between 18 and 75 years. Postoperative duration of 24 hours.	91% (183 of the 201 participants. 18 excluded following deviations from the inclusion criteria).	Group 1 (Nefopam Group)—Nefopam (20 mg after every 4 over a 24-hour duration) Group 2 (Placebo group)—control.	16 weeks	France	Prospective, double-blind, randomized trial report.
Article 3	Kapfer *et al.* [19]	77 patients, male and female, 18–65 years old.	87% (65 out of 77 participants included in the analysis)	Group 1—Isotonic saline (Control) Group 2—Ketamine 10 mg (Ketamine) Group 3—Nefopam 20 mg (Nefopam)	17 weeks	USA	Randomized controlled trial
Article 4	Evans *et al.* [5]	847 participants, male and female, aged above 18.	100% (All 847 participants were randomized and responded to treatment).	Group 1—Nefopam Group 2—Another analgesic (ketamine, diclofenac, paracetamol, tilidine, or propoxyphene). Group 3—Inactive control treatment.	9 weeks.	France, United Kingdom, Belgium, and USA.	Quantitative systematic review
Article 5	Richebé *et al.* [20]	90 participants, male and female, aged above 18 years. Postoperative duration: 48 hours.	100% (90 respondents)	Group 1 (G1)—0.3 mg/kg bolus of nefopam at the start of anesthesia, followed by continuous infusion of 0.065 mg/kg/hour for 48 hours. Group 2 (G2)—0.3 mg/kg bolus of nefopam at the end of surgery, followed by continuous infusion of 0.065 mg/kg/hour for 48 hours. Group 3 (G3)—Placebo.	36 months	United States	Randomized prospective study.
Article 6	Kim *et al.* [11]	300 participants, male and female, aged 20 years and above. Postoperative duration assessed intermittently for 72 hours.	92% (276 out of 300 participants completed the trial).	Group 1—PCA with Nefopam (300 mg nefopam 2 mg/ml + 0.6 mg ramosetron for nausea prevention) Group 2—PCA with Fentanyl (1,500 µg fentanyl + 0.6 mg ramosetron) Group 3—PCA with Nefopam + Fentanyl (140 mg nefopam + 700 µg fentanyl + 0.6 mg ramosetron)	4 weeks	Republic of Korea	Randomized prospective study.

(continued)

Article number	Author & publication year	Participants (Age, gender, duration of postoperative period)	Response ratio (Number of respondents)	Study groups and interventions s	Study duration	Study country	Publication type
Article 7	Choi *et al.* [1]	54 participants, Female and male, between 18 and 70 years old.	100%	Nefopam (N Group)—nefopam. Ketamine (K Group)—ketamine. Control group—standard anesthetic regimen.	24 weeks	South Korea	Randomized prospective study.
Article 8	Girard *et al.* [8]	10 studies included for review. Total number of participants are not provided.	100% (all 10 studies reviewed)	Different groups in respective studies.	6 weeks.	Universal.	Systematic review of preclinical and clinical studies.
Article 9	Moon *et al.* [21]	90 participants, female, 18–70 years of age. 48-hour postoperative period.	90% (81 out of 90 participants).	Group A—Fentanyl 1,000 µg. Group B—Fentanyl 500 µg + nefopam 200 mg Group C—Fentanyl 500 µg + nefopam 400 mg. All treatments were administered via 100 ml PCA over the first 48 hours postoperatively.	1 year from November 2011	Korea Republic	Randomized double-blind study.
Article 10	Son *et al.* [22]	160 patients, male and female, aged 20–70 years. Postoperative duration: 48 hours.	89% (142 out of the 160 patients assessed for eligibility were analyzed).	Group K (Ketorolac group)—Analgesic solution containing fentanyl 600 µg + ketorolac 180 mg. Group N (Nefopam group) – Analgesic solution containing fentanyl 600 µg + nefopam 120 mg.	8 weeks	South Korea	Randomized, double-blind prospective study.
Article 11	Zhao *et al.* [15]	215 patients analyzed across 4 random-controlled trials. Average age for patients was 41–50 years old.	100% (215 respondents).	Group 1 (Intervention group)—Nefopam 20 mg. Group 2 (control group)—Normal saline.	Not specified.	USA	Meta-analysis
Article 12	Nair [23]	83 participants observed in a separate study. Additional information on age, gender, and postoperative duration missing.	100%	Group 1—20 mg IV nefopam Group 2—Placebo (normal saline)	4 weeks	Korea Republic	Prospective, double blind, randomized trial report addressed to the editor.
Article 13	Pasutharnchat *et al.* [25]	40 participants, Over 18 years of age, male and female	100% (all 40 participants passed the inclusion criteria and were assessed in two groups)	Nefopam group—20 mg of nefopam in 100 ml normal saline (NSS), intravenously through an infusion pump for 30 minutes, after every 8 hours during the 24-hour study duration. Placebo group—100 ml NSS using the same protocol as the nefopam group.	16 weeks	Thailand	Randomized, double-blind prospective study.

(continued)

Article number	Author & publication year	Participants (Age, gender, duration of postoperative period)	Response ratio (Number of respondents)	Study groups and interventions s	Study duration	Study country	Publication type
Article 14	Lekprasert *et al.* [26]	72 participants, male and female, aged 20–65 years. Postoperative duration: 24 hours.	99% (71 out of 72 patients. 1 excluded due to patient refusal).	Group 1 (Study group)—Parecoxib 40 mg + Nefopam 20 mg. Group 2 (Control group)—Parecoxib 40 mg + normal saline solution).	6 weeks	Thailand	Randomized, double-blind, prospective study.
Article 15	Jung *et al.* [12]	78 patients, male and female, 20–70 years. 24-hour postoperative duration.	90% (A dropout rate of approximately 10%).	Group NF—PCA with combination of fentanyl 600 µg and nefopam 120 mg (nefopam-fentanyl polytherapy). Group N240—PCA with nefopam 240 mg alone (nefopam monotherapy).	12 weeks	South Korea	Randomized, double-blind, prospective study.
Article 16	Chalermkitpanit *et al.* [27]	100 patients, aged between 20 and 80 years, male and female.	100% (all 100 patients assessed)	Nefopam Group—20 mg of intravenous nefopam diluted in 100 ml of normal saline. Control Group—100 ml of normal saline.	15 months	Thailand	Randomized, double-blind study.
Article 17	Yoon *et al.* [28]	90 patients. male and female, aged 19–70 years.	100%	Group N (Nefopam)—20 mg nefopam. Group C (Control)—Normal saline.	3 months	South Korea	Randomized, double-blind study.

Table 2. Summary of average reduction in opioid consumption and CIs.

Study	% Reduction in opioid consumption	CIs
Mimoz *et al.* [6]	50%	0.05 to 0.41
du Manoir *et al.* [4]	40%	0.15 to 0.72
Evans *et al.* [5]	25%	−1.62 to 0.785
Richebé *et al.* [20]	50%	−1.296 to −0.176
Kim *et al.* [11]	30%	0.952 to 2.743
Moon *et al.* [21]	40%	−1.16 to 0.76
Zhao *et al.* [15]	35%	−0.05 to −1.27
Pasutharnchat *et al.* [25]	30%	0.15 to 0.52
Jung *et al.* [12]	40%	−0.73 to 0.63

The overall range of confidence intervals (CI) from all the readings is −1.62. to 2.743.

Overall, this systematic review showed that nefopam generally reduced opioid consumption in postoperative patients. No adverse effects were reported in 9 of the 17 studies. In the remaining seven studies, various adverse effects were reported, mostly in the treatment groups, but with a relatively low frequency. The results of the individual studies are summarized in Table 3.

Quality assessment and ROB

Cochrane's ROB-2 tool was used to assess the ROB in individual studies. Based on the ROB assessment, the overall quality of the included articles was good. Only one article [23] had a high risk. The majority of the remaining 16 articles had low risk. A summary of the assessment performed is presented in Table 4 for each study, based on the average of the authors' ratings.

A high ROB was reported in the report by Nair [23] because the summative report had no explicit research methods included. However, the report was important in the current study as it also contributed knowledge on the use of nefopam in postoperative pain management. The overall goal of the current study was to find literature surrounding the topic and evaluate evidence in line with the set objectives. Therefore, while some of the domains included in Cochrane's ROB-2 tool revealed some issues creating the bias, it was still included as a relevant source of literature given that it was a report of a previous study.

Impact of nefopam on opioid consumption

This review found a significant decrease in opioid consumption in 12 of the 17 studies, whereas the remaining 5 studies found no significant difference in opioid consumption between the nefopam and control groups. Of the 12 studies that reported reductions in opioid consumption, 9 reported specific percentage reduction values as follows: Mimoz *et al.* [6]—50%, du Manoir *et al.* [4]—40%, Evans *et al.* [5]—25%, Richebé *et al.* [20]—50%, Kim *et al.* [11]—30%, Moon *et al.* [21]—40%, Zhao *et al.* [15]—35%, Jung *et al.* [12]—40%, Pasutharnchat *et al.* [25]—30%. Based on the above values from studies reporting specific values, the

Table 3. Results summary for included studies.

Article number	Study groups and interventions	Postoperative pain indicators	Opioid consumption indicators	Impact on opioid consumption	% Reduction in opioid consumption	Patient satisfaction with treatment	Safety and incidence of adverse events
Article 1 Mimoz *et al.* [6]	Group 1 (Control group)—PCA morphine alone. Group 2 (Nefopam group)—PCA morphine + nefopam 20 mg after every 4 hours. Group 3 (Propacetamol group)—PCA morphine + propacetamol 2 g every 6 hours.	VAS both at rest (VAS-R) and when coughing (VAS-C)	Morphine equivalents	Total morphine consumption significantly lower in the nefopam group compared to the two other groups.	50%	Patients highly satisfied with the treatment.	No adverse effects were reported in all three groups.
Article 2 du Manoir *et al.* [4]	Group 1 (Nefopam Group)—Nefopam (20 mg every 4 hours for 24 hours) Group 2 (Placebo group)—Control.	VAS and Virtual Pain Scale (VPS)	Morphine equivalents	PCA-administered morphine significantly less for the nefopam group as compared to the control group.	40%	Patients' satisfaction similar for nefopam and placebo groups.	No adverse effects were reported in the study group and the placebo group.
Article 3 Kapfer *et al.* [19]	Group 1—Isotonic saline (Control) Group 2—Ketamine 10 mg (Ketamine) Group 3—Nefopam 20 mg (Nefopam)	Five-point VRS	Morphine equivalents	Supplemental morphine requirements significantly higher in the control group than the nefopam group.	Not stated	Patients relatively satisfied with the treatment.	Tachycardia and profuse sweating reported in 6 patients in the nefopam group. No adverse effects reported in the control group.
Article 4 Evans *et al.* [5]	Group 1—Nefopam Group 2—Another analgesic (ketamine, diclofenac, paracetamol, tilidine, or propoxyphene). Group 3—Inactive control treatment.	VAS/Visual Analog Pain Scale (VAPS)	Morphine consumption equivalents.	Morphine consumption reduced with nefopam.	25%	Improved patient satisfaction for the nefopam group with reduced morphine consumption.	Postoperative tachycardia was reported in two patients in Group 1 and Group 2. One patient in the placebo group had profuse sweating.
Article 5 Richebé *et al.* [20]	Group 1 (G1)—0.3 mg/kg bolus of nefopam at the start of anesthesia, followed by continuous infusion of 0.065 mg/kg/hour for 48 hours. Group 2 (G2)—0.3 mg/kg bolus of nefopam at the end of surgery, followed by continuous infusion of 0.065 mg/kg/hour for 48 hours. Group 3 (G3)—Placebo	Von Frey Filaments	Morphine consumption equivalents	Reduced morphine equivalents	50%	Patient satisfaction with treatment not stated.	No adverse effects were reported in all the study groups.

(continued)

Article number	Study groups and interventions	Postoperative pain indicators	Opioid consumption indicators	Impact on opioid consumption	% Reduction in opioid consumption	Patient satisfaction with treatment	Safety and incidence of adverse events
Article 6 Kim *et al.* [11]	Group 1—PCA with Nefopam (300 mg nefopam 2mg/ml + 0.6 mg ramosetron for nausea prevention) Group 2—PCA with Fentanyl (1,500 µg fentanyl + 0.6 mg ramosetron) Group 3—PCA with Nefopam + Fentanyl (140 mg nefopam + 700 µg fentanyl + 0.6 mg ramosetron)	VAS both at rest (VAS_R) and in movement (VAS_M).	Fentanyl equivalents	Reduced fentanyl use in the Fentanyl + Nefopam group.	30%	Patients satisfied with administered treatment.	Tachycardia, respiratory depression, sedation, and other common postoperative outcomes like nausea and vomiting were reported in some patients in the two treatment groups as well as the control group.
Article 7 Choi *et al.* [1]	Nefopam (N Group)—nefopam. Ketamine (K Group)—ketamine. Control group—standard anesthetic regimen.	VAS	Morphine equivalents.	Co-administered nefopam or ketamine significantly lowered the consumption of remifentanil and morphine.	Not stated	Patients highly satisfied with the treatment.	No critical effects reported in either group.
Article 8 Girard *et al.* [8]	Different groups in respective studies.	Pain scores with a linear pain scale such as VAS, VRS, or NRS.	Morphine equivalents.	8 out of 10 studies reported reduced postoperative morphine consumption.	Not stated	Patients' satisfaction reported in studies that showed reduced morphine consumption.	No adverse effects discussed in the article.
Article 9 Moon *et al.* [21]	Group A—Fentanyl 1,000 µg. Group B—Fentanyl 500 µg + nefopam 200 mg Group C - Fentanyl 500 µg + nefopam 400 mg. All treatments were administered via 100 ml PCA over the first 48 hours postoperatively.	Verbal pain score	Fentanyl consumption equivalents.	No significant differences in fentanyl consumption in the three study groups. However, overall sedation was lower in Group B.	40%	Patients satisfied with the treatment.	No adverse side effects reported in Group A, Group B, and Group C.
Article 10 Son *et al.* [22]	Group K (Ketorolac group)—Analgesic solution containing fentanyl 600 µg + ketorolac 180 mg. Group N (Nefopam group)—Analgesic solution containing fentanyl 600 µg + nefopam 120 mg.	NRS	Fentanyl equivalents	Reduced fentanyl consumption after 24 hours of postoperative administration.	Not stated	Patients relatively satisfied with the procedure.	Post-operative nausea and vomiting, with minimal incidence of other postoperative adverse effects were reported in three patients in the Group K and Group N.

(continued)

Article number	Study groups and interventions	Postoperative pain indicators	Opioid consumption indicators	Impact on opioid consumption	% Reduction in opioid consumption	Patient satisfaction with treatment	Safety and incidence of adverse events
Article 11 Zhao *et al.* [15]	Group 1 (Intervention group)—Nefopam 20 mg. Group 2 (control group)—Normal saline.	VAS	Morphine equivalents	No significant difference in opioid consumption between the two groups.	35%	Patients relatively satisfied with the intervention.	Pruritus, nausea, and vomiting were relatively mild in the nefopam group and the control group.
Article 12 Nair [23]	Group 1—20 mg IV nefopam Group 2—Placebo (normal saline)	NRS	Nefopam equivalents.	Reduced opioid consumption and lowered chronic pain after 3 months.	Not stated	Patients satisfied with the treatment.	No adverse effects reported in the nefopam group and control (placebo) group.
Article 13 Pasutharnchat *et al.* [25]	Nefopam group—20 mg of nefopam in 100 ml normal saline (NSS), intravenously through an infusion pump for 30 minutes, after every 8 hours during the 24-hour study duration. Placebo group—100 ml normal saline solution (NSS) using the same protocol as the nefopam group.	NRS (Patients were trained on how to use a 0 – 10 pain rating scale).	Morphine equivalents (Median dosage of morphine consumption)	A trend toward reduction of opioid consumption was shown in the nefopam group.	30%	Patients satisfied with intervention.	Side effects including nausea, dizziness, dry mouth, sweating, vomiting, drowsiness, and tachycardia were low in both the nefopam group and placebo group.
Article 14 Lekprasert *et al.* [26]	Group 1 (Study group)—Parecoxib 40 mg + Nefopam 20 mg. Group 2 (Control group)—Parecoxib 40 mg + normal saline solution).	Verbal Numerical Rating Scale (VNRS)	Morphine equivalents	Morphine consumption not significantly different in both groups.	Not stated	Patients' satisfaction similar in both groups.	No adverse effects save for nausea and vomiting in 2 patients in the study group.
Article 15 Jung *et al.* [12]	Group NF—PCA with combination of fentanyl 600 µg and nefopam 120 mg (nefopam-fentanyl polytherapy). Group N240—PCA with nefopam 240 mg alone (nefopam monotherapy).	NRS	Fentanyl equivalents	No significant difference in consumption of fentanyl.	40%	Patient satisfaction with treatment not reported.	No postoperative adverse effects were reported in both groups, save for postoperative nausea and vomiting (PONV), whose incidence was high in Group NF.
Article 16 Chalermkitpanit *et al.* [27]	Nefopam group - 20 mg of intravenous nefopam diluted in 100 ml of normal saline. Control group—100 ml of normal saline	NRS	Morphine equivalents.	No significant differences in total morphine consumption and postoperative pain between the two groups.	Not stated	Patient satisfaction with treatment not specified.	No serious adverse effects of nefopam were reported.
Article 17 Yoon *et al.* [28]	Group N (Nefopam)—20 mg nefopam over 30 minutes, for 24 hours. Group C (Control)—Normal saline, same volume.	Verbal pain rating scale.	Fentanyl consumption equivalents	Group N had significantly lower fentanyl consumption compared to Group C in the first 24 hours.	Not stated	Patients satisfied with the treatment.	Nausea, vomiting, rescue anti-emetic use, and hydrosis reported in an almost even proportion between the nefopam group and control group.
Average					38%		

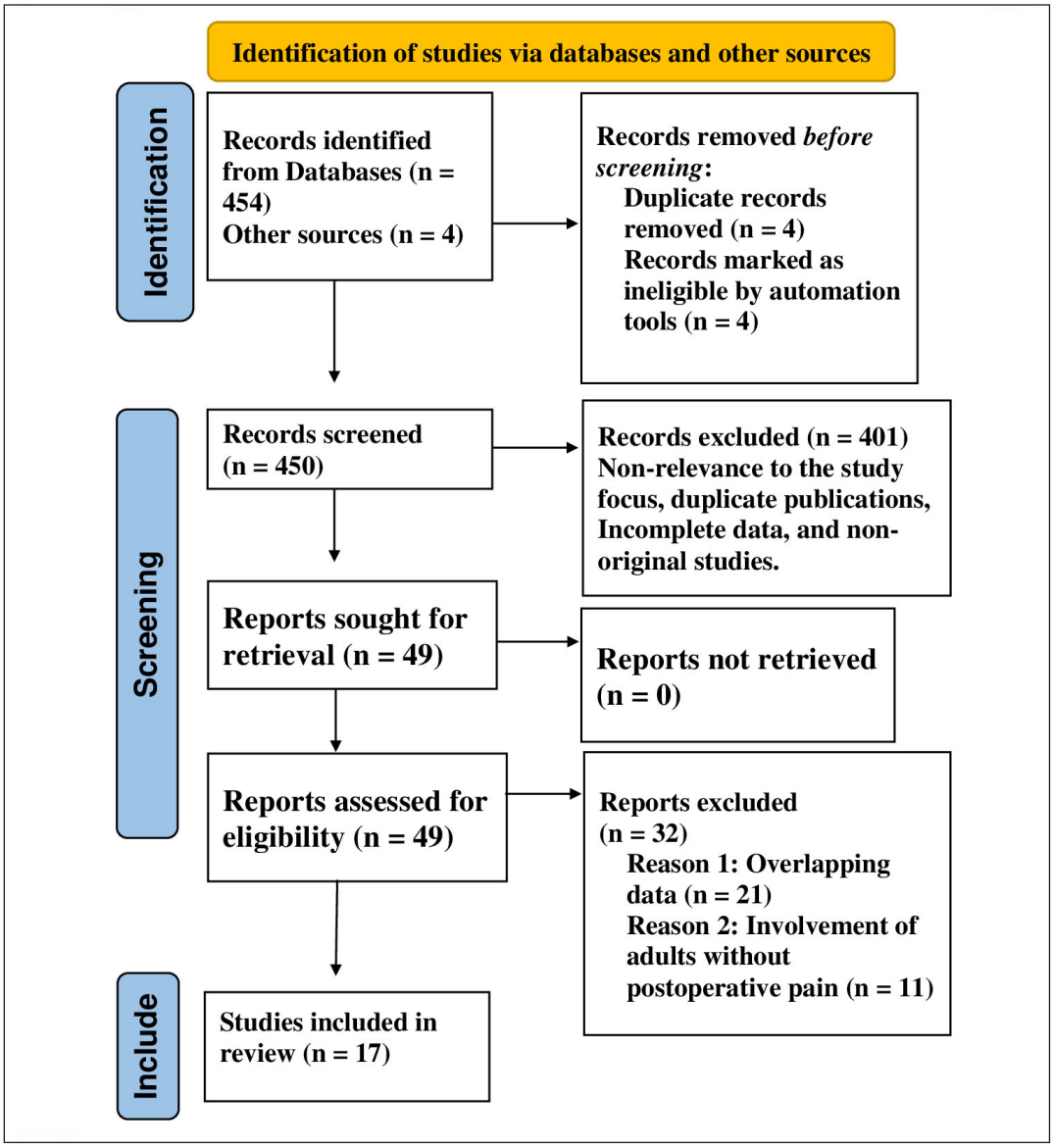

Figure 1. PRISMA flow diagram of the systematic review strategy.

summary of the calculation of the percentage reduction in opioid use is: (50+40+25+50+30+40+35+40+30)/9 = 37.77 ≈ 38%. The average reduction in opioid consumption due to the postoperative use of nefopam was, therefore, 38%.

The reported percentage decrease in opioid consumption ranged from 25% to 50% across the studies. This variation could be attributed to differences in study populations, interventions, and methodologies. Some studies had confidence intervals (CIs) that included zero or negative values, suggesting that the observed effect may not be statistically significant or may favor the control group as shown in Table 2. The overall range of CIs from all the readings was (−1.62–2.743). The forest plot in Figure 2 also shares findings of the calculated CIs. While most studies reported a positive effect (reduction in opioid consumption), some studies, such as Evans *et al.* [5] and Richebé *et al.* [20], had CIs that included negative values, suggesting the possibility of increased opioid consumption or no effect. More recent studies such as Moon *et al.* [21], Zhao *et al.* [15]), Pasutharnchat *et al.* [25], and Jung *et al.* [12], generally showed a consistent trend of decreased opioid consumption, with narrower CIs, indicating more precise estimates of the effect. Overall, the results indicate that the treatments or interventions evaluated in these studies may reduce opioid consumption, but the magnitude of the effect varies across studies, as shown in the forest plot in Figure 2.

The study also showed that nefopam administration was associated with pain reduction in most patients. While the included studies used different pain scores, including Verbal analogue scale (VAS), Verbal Rating Scale (VRS), NRS, and Verbal analogue scale at rest (VAS-R), most of the studies reported that patients had better pain relief when postoperative

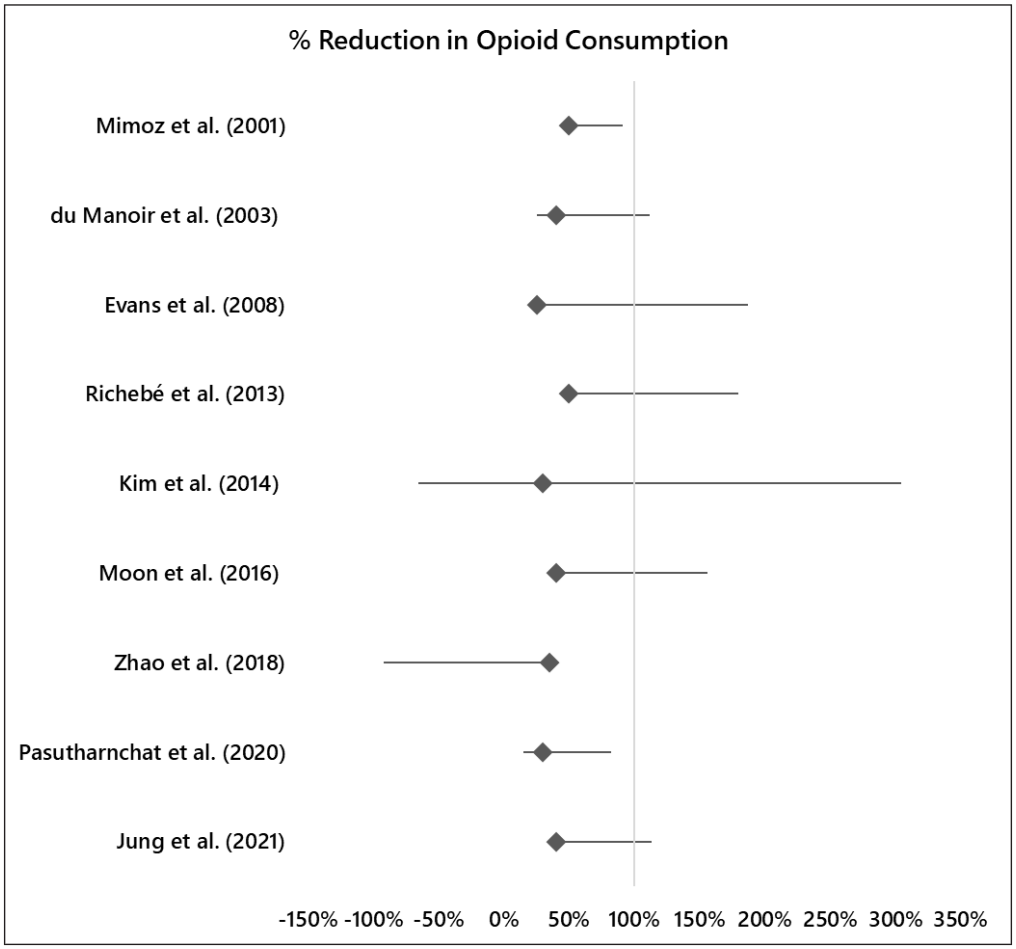

Figure 2. Forest plot for reduction in opioid consumption.

nefopam was administered. Using NRS, Jung *et al.* [12], Moon *et al.* [21], and Son *et al.* [22] all reported scores below 5, showing significant pain reduction in the nefopam groups [27,29]. Both Choi *et al.* [1] and Zhao *et al.* [15] also recorded reduced pain scores using the VAS [22,26]. However, Kapfer *et al.* [19] indicated that there were no major differences between the nefopam group and the control group when pain scores were measured using VRS.

Patient satisfaction with treatment

Most patients were satisfied with the treatment administered. In 13 out of the 17 studies included in the review, patient satisfaction was reported, ranging from moderate to significantly high levels of satisfaction with the use of nefopam in postoperative pain management. Two studies did not report the eventual level of satisfaction, while the remaining two studies reported similar satisfaction levels between the treatment group and the control group. As such, the researcher concluded that nefopam administration in postoperative pain management is positively correlated with patient satisfaction.

Safety and incidence of adverse effects

No adverse effects were reported in 9 out of the 17 studies. In the remaining seven studies, various adverse effects were reported, mostly in the treatment groups but with a relatively low incidence. The most common adverse effects included tachycardia, sweating, nausea, and drowsiness. Two pruritus cases were also reported in one of the studies, with one case of respiratory depression also reported. Hypoventilation, malaise, and general cutaneous allergy also occurred in three patients in the treatment group of one of the randomized controlled studies. In cases where nausea, vomiting, and sweating were reported, the cases were relatively mild. However, there were cases of profuse sweating in two participants.

DISCUSSION

Nefopam use in postoperative pain management

Although opioids have long been used in postoperative pain management, the prevalence of associated side effects has led to increased research into non-opioid analgesics. According to Stephan and Parsa [30], opioid analgesics relieve postoperative pain but also have distressing negative effects on the body. Opioids not only impair the release of μ opioid receptors but also prevent the release of beta-endorphin, which is crucial for pain management. In addition, Li *et al.* [31] noted that opioids complicate pain management by causing adverse effects such as postoperative nausea/vomiting,

Table 4. ROB assessment.

Study	D1a	D1b	D2	D3	D4	D5	Overall
Mimoz *et al.* [6]	!	+	+	+	+	+	+
du Manoir *et al.* [4]	+	!	+	+	!	+	!
Kapfer *et al.* [19]	+	+	+	+	-	+	!
Evans *et al.* [5]	+	+	+	+	!	+	+
Richebé *et al.* [20]	!	!	+	+	+	+	!
Kim *et al.* [11]	!	!	+	+	+	+	+
Choi *et al.* [1]	+	+	+	+	!	+	+
Girard *et al.* [8]	!	!	+	+	!	+	!
Moon *et al.* [21]	+	+	+	+	+	+	+
Son *et al.* [22]	+	+	+	+	+	+	+
Zhao *et al.* [15]	!	-	!	+	+	+	!
Nair [23]	-	-	-	+	!	!	-
Pasutharnchat *et al.* [25]	!	+	!	+	+	+	+
Lekprasert *et al.* [26]	+	+	!	+	+	+	+
Jung *et al.* [12]	+	+	+	+	+	+	+
Chalermkitpanit *et al.* [27]	+	+	+	!	+	+	+
Yoon *et al.* [28]	+	+	+	!	+	!	+

pruritus, respiratory depression, and urinary retention. Because of the adverse side effects of opioids, multimodal analgesia is increasingly being considered for postoperative pain management, including various approaches such as preemptive analgesia, PCA, neuraxial anesthesia, and non-opioid medications.

Another important problem in the postoperative use of opioids is neuroadaptation. According to Lavand'homme and Steyaert [29], while opioids are the most effective drugs currently used to treat chronic pain, they have limited ability to provide long-term analgesia due to neuroadaptation. Further evidence suggests that neuroadaptation occurs mainly through opioid-induced hyperalgesia and tolerance [29]. In some cases, opioids also have opposite effects, such as enhancing postoperative pain. To mitigate the potential occurrence of neuroadaptation and opposite effects, different

Table 5. Incidence of adverse effects.

Article number	Incidence of adverse events
Article 1 Mimoz *et al.* [6]	No adverse effects were reported in all three groups.
Article 2 du Manoir *et al.* [4]	No adverse effects were reported in the study group and the placebo group.
Article 3 Kapfer *et al.* [19]	Tachycardia and profuse sweating reported in six patients in the nefopam group. No adverse effects reported in the control group.
Article 4 Evans *et al.* [5]	Postoperative tachycardia was reported in two patients in Groups 1 and 2. One patient in the placebo group had profuse sweating.
Article 5 Richebé *et al.* [20]	No adverse effects were reported in all the study groups.
Article 6 Kim *et al.* [11]	Tachycardia, respiratory depression, sedation, and other common postoperative outcomes like nausea and vomiting were reported in some patients in the two treatment groups as well as the control group.
Article 7 Choi *et al.* [1]	No critical effects reported in either group.
Article 8 Girard *et al.* [8]	No adverse effects discussed in the article.
Article 9 Moon *et al.* [21]	No adverse side effects reported in Group A, Group B, and Group C.
Article 10 Son *et al.* [22]	Post-operative nausea and vomiting, with minimal incidence of other postoperative adverse effects were reported in three patients in the Group K and Group N.
Article 11 Zhao *et al.* [15]	Pruritus, nausea, and vomiting were relatively mild in the nefopam group and the control group.
Article 12 Nair [23]	No adverse effects reported in the nefopam group and control (placebo) group.
Article 13 Pasutharnchat *et al.* [25]	Side effects including nausea, dizziness, dry mouth, sweating, vomiting, drowsiness, and tachycardia were low in both the nefopam group and placebo group.
Article 14 Lekprasert *et al.* [26]	No adverse effects save for nausea and vomiting in two patients in the study group.
Article 15 Jung *et al.* [12]	No postoperative adverse effects were reported in both groups, save for postoperative nausea and vomiting (PONV), whose incidence was high in Group NF.
Article 16 Chalermkitpanit *et al.* [27]	No serious adverse effects of nefopam were reported.
Article 17 Yoon *et al.* [28]	Nausea, vomiting, rescue anti-emetic use, and hydrosis reported in an almost even proportion between the nefopam group and control group.

opioids, dose limitations, and non-opioid analgesics can be used [32].

Nefopam exerts its analgesic effect through various pharmacological mechanisms. Its central analgesic effect helps to modulate pain perception by acting centrally in the brain and spinal cord [8]. Some of the key attributes include preventing the reuptake of neurotransmitters such as norepinephrine, dopamine, and serotonin, increasing their concentration in the synaptic cleft, thereby enhancing various descending inhibitory pain pathways [8]. Although nefopam's analgesic effect is primarily centrally mediated, it also has a peripheral analgesic effect by inhibiting the release of inflammatory mediators and prostaglandins. Nefopam also exhibits N-Methyl-D-aspartate (NMDA) receptor antagonism, which modulates pain perception and reduces the transmission of pain signals by blocking NMDA receptors [31]. Overall, the above pharmacological mechanisms enhance nefopam's pain relief abilities while reducing opioid consumption, as revealed by findings of the current study involving postoperative patients.

The current study found that nefopam is a viable non-opioid analgesic for postoperative pain management. Recent studies on the efficacy of nefopam in postoperative pain management suggest that patients' pain is reduced due to the morphine-sparing effect of nefopam [28]. In this systematic

review, nefopam significantly reduced opioid consumption in postoperative patients, justifying its morphine-sparing effect. The mean decrease in opioid consumption across studies was 38%. Overall, the attained average figure suggests that patients receiving nefopam to supplement an analgesic regimen with opioids are likely to experience almost as much reduction in pain intensity as patients receiving high doses of opioids. Thirteen studies reported lower opioid consumption when nefopam was administered postoperatively. In the studies that reported pain reduction, there was a strong statistical correlation between nefopam use, reduced morphine consumption, and pain reduction in participating patients. In contrast, five studies reported no significant difference in opioid consumption and postoperative pain management after nefopam administration [12,15,21,26,27].

In addition, the overall analgesic effect of nefopam was found to be superior to that of opioids alone. Greater pain relief was reported in cases where nefopam was co-administered with other analgesic adjuvants such as acetaminophen [6] and fentanyl [22,29], as well as ketamine [1]. Because the doses of nefopam administered varied, researchers were unable to identify specific doses associated with nefopam's morphine-sparing effects. In the past, the role of nefopam in the management of postoperative pain has been questioned because of the limited characterization of the regimens and doses used, particularly in combination with other analgesic adjuvants [2].

Previous studies examining the analgesic effects of nefopam have shown that it has nearly similar efficacy compared with opioid alternatives. According to Tramoni *et al.* [33], 20 mg of nefopam shows efficacy equivalent to that of 6–12 mg of morphine. Yoon *et al.* [28] also indicated that 20 mg of nefopam is equivalent to about 7.5 mg of ketorolac and morphine in postoperative pain control [28]. In sum, the results of the current study are consistent with the existing literature on analgesic efficacy. For example, du Manoir *et al.* [4] and Evans *et al.* [5] found that the analgesic efficacy of nefopam was comparable to that of other opioids [4,5]. However, opioids were more likely to cause adverse effects in patients than non-opioid analgesics.

A study conducted by Tramoni *et al.* [33] indicated that nefopam reduced opioid consumption by up to 50%, but the average reduction was about 25%. The findings are consistent with the results of most of the studies included in the analysis. For example, du Manoir *et al.* [4] reported a 40% reduction in opioid consumption when 20 mg of nefopam was infused every 4 hours [4]. Evans *et al.* [5] found that infusion of nefopam resulted in a 25% reduction in opioid consumption compared with the control group, which had no change in opioid consumption [5]. According to Richebé *et al.* [20], continuous nefopam infusion resulted in a 50% reduction in opioid consumption in the nefopam group. Based on the results of the current analysis, it can be concluded that nefopam could reduce opioid consumption by up to 50%, depending on the amount administered to patients.

Safety and incidence of adverse effects

Based on the observed adverse effects, this systematic review found that co-administration of nefopam is generally well tolerated by patients. The overall trend of adverse effects was generally low. In studies that reported adverse effects, nausea, sweating, and postoperative tachycardia were common. However, the outcomes were mostly classified as uncomfortable and not significant medical problems. These findings are consistent with existing literature. According to Charoenpol *et al.* [2], co-administration of nefopam in the management of moderate pain is often associated with a minimal incidence of adverse effects.

The common adverse effects of nefopam that have been document in previous research include nausea, vomiting, hypotension, tachycardia, sedation, sweating, respiratory depression, itching, urinary retention, and dry mouth [2]. Compared to opioids used in postoperative pain management, the tendency of adverse effects following nefopam administration is generally lower. This is partly attributed to its central analgesic effect that is associated with minimal unwanted reactions in other parts of the body [2]. As revealed in the current study, the occurrence of adverse effects for most treatment groups given nefopam was generally lower as compared to groups given opioids and other analgesics, as shown in Table 5.

Chalermkitpanit *et al.* [27] believe that nefopam is increasingly used in the management of postoperative pain because it has minimal adverse effects on patients, with postoperative nausea and vomiting, sweating, and tachycardia being the most observed adverse effects [27]. In the current review, the studies by Jung *et al.* [12] and Lekprasert *et al.* [26] showed that most patients had few adverse effects in their respective treatment groups [12,26]. However, postoperative tachycardia can be dangerous in patients with impaired cardiac function [34].

Patient satisfaction with the treatment

This review found that concomitant administration of nefopam resulted in pain relief in most patients. A variety of pain scales were used in the included studies, including the VAS, the VRS, the NRS, and the VAS-R. Most studies indicated that patients experienced better pain relief when nefopam was co-administered postoperatively with other analgesics. Jung *et al.* [12], Moon *et al.* [21], and Son *et al.* [22] reported NRS scores below five, which showed significant pain reduction in the nefopam groups [12,21,22]. Both Choi *et al.* [1] and Zhao *et al.* [15] also recorded reduced pain scores using the VAS [1,15]. However, Kapfer *et al.* [19] pointed out that there were no significant differences between the nefopam group and the control group when pain scores were measured using the VRS [19]. The current study found that most patients were satisfied with the treatment. Finally, the low incidence of adverse effects of nefopam also resulted in a high level of satisfaction among most patients.

LIMITATIONS

At the study level, this systematic review did not assess outcomes for patients receiving combination therapy of nefopam and different types of opioids and also excluded studies of patients receiving long-term postoperative pain therapy, which could provide valuable insights into the effects of nefopam on opioid consumption in postoperative patients.

At the review level, adverse effects were not discussed in detail in the included studies. Factors such as the type of surgery, dosage and timing of nefopam administration, and the corresponding influences on opioid consumption may have been incompletely investigated.

CONCLUSION AND FUTURE IMPLICATIONS

This study offers a general interpretation of the results in the context of existing evidence and provides implications for future research. The systematic review demonstrated that nefopam is effective in postoperative pain management, as evidenced by lower pain scores and lower morphine consumption in postoperative patients. Specifically, the results suggest that nefopam significantly reduces opioid consumption with a relatively low incidence of side effects. Future research is needed to further investigate the potential of nefopam as an alternative to opioids to reduce opioid consumption in postoperative patients, as well as the potential influence of factors such as type of surgery, dosage, and timing of administration on the effect of nefopam on opioid consumption. Future studies could also examine comparative effectiveness in long-term postoperative pain management, particularly examining pain intensity and the duration of analgesic effect. Additionally, combination therapy studies could be conducted to evaluate the synergic effects of nefopam with other analgesics. Finally, there is still a significant literature gap regarding the pharmacokinetic and pharmacodynamic properties of nefopam. Profiling nefopam based on these properties could avail further understanding of its mechanisms of action as well as the overall influence on reduction in opioid consumption when used postoperatively.

LIST OF ABBREVIATIONS

NRS, Numeric Rating Scale; NSAIDs, Non-steroidal anti-inflammatory drugs; PCA, Patient-controlled analgesia; RCTs, Randomized-controlled trials; VAS, Verbal analogue scale; VAS-R, Verbal analogue scale at rest; VRS, Verbal rating scale.

AUTHOR CONTRIBUTION

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

FINANCIAL SUPPORT

There is no funding to report.

CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

Not applicable.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

PUBLISHER'S NOTE

All claims expressed in this article are solely those of the authors and do not necessarily represent those of the publisher, the editors and the reviewers. This journal remains neutral with regard to jurisdictional claims in published institutional affiliation.

USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

LIST OF VARIABLES

The variables for which data were sought are listed and defined below:

Nefopam administration—The main aim of the study was to assess the role of nefopam in reducing opioid consumption in postoperative patients. Therefore, postoperative nefopam administration, either on a singular method or in combination with other analgesics was examined.

Opioid consumption—Traditional approach for treatment of acute postoperative pain, involving administration of various opioid analgesics such as morphine and fentanyl.

Occurrence of adverse effects—outcomes such as vomiting, sweating, and tachycardia, associated with postoperative administration of nefopam and alike analgesics.

Overall patient satisfaction with treatment—assessment of the extent of satisfaction based on pain reduction, opioid consumption, and the occurrence of side effects.

REFERENCES

1. 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.
2. Charoenpol FN, Khampitak N, Aimnang C, Pachirat K, Sirithanaphol W, Rompsaithong U, *et al*. Single-dose intravenous nefopam on postoperative catheter-related bladder discomfort in patients undergoing transurethral resection of prostate: a randomized, double-blind placebo-controlled trial. J Anesth. 2023;37(1):72–8.
3. Franzese A, Borrelli O, Corrado G, Rea P, Di Nardo G, Grandinetti AL, *et al.* Domperidone is more effective than cisapride in children with diabetic gastroparesis. Aliment Pharmacol Ther. 2002;16:951–7. doi: https://doi.org/10.1046/j.1365-2036.2002.01240.x
4. 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 [Internet]. 2003 [cited 2023 Jan 5];91(6):836–41. Available from: https://pubmed.ncbi.nlm.nih.gov/14633755/
5. Evans MS, Lysakowski C, Tramèr MR. Nefopam for the prevention of postoperative pain: quantitative systematic review. Br J Anaesth. 2008;101(5):610–7.
6. Mimoz O, Incagnoli P, Josse C, Gillon MC, Kuhlman L, Mirand A, *et al.* Analgesic efficacy and safety of nefopam vs. propacetamol following hepatic resection. Anaesthesia. 2001;56(6):520–5.

7. Mitra S, Carlyle D, Kodumudi G, Kodumudi V, Vadivelu N. New advances in acute postoperative pain management. Curr Pain Headache Rep. 2018;22:1.
8. 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.
9. Hariton E, Locascio JJ. Randomised controlled trials—the gold standard for effectiveness research. BJOG. 2018;125(13):1716.
10. Kim KH, Abdi S. Rediscovery of nefopam for the treatment of neuropathic pain. Korean J Pain [Internet]. 2014 [cited 2023 Jan 5];27(2):103. Available from: /pmc/articles/PMC3990817/
11. Kim K, Kim WJ, Choi DK, Lee YK, Choi IC, Sim JY. The analgesic efficacy and safety of nefopam in patient-controlled analgesia after cardiac surgery: a randomized, double-blind, prospective study. J Int Med Res [Internet]. 2014 [cited 2023 Jan 5];42(3):684–92. Available from: http://www.uk.sagepub.com/aboutus/openaccess.htm
12. Jung KT, So KY, Kim SC, Kim SH. Effect of nefopam-based patient-controlled analgesia with and without fentanyl on postoperative pain intensity in patients following laparoscopic cholecystectomy: a prospective, randomized, controlled, double-blind non-inferiority trial. Medicina [Internet]. 2021 [cited 2023 Jan 5];57(4):316. Available from: https://www.mdpi.com/1648-9144/57/4/316
13. Martinez V, Beloeil H, Marret E, Fletcher D, Ravaud P, Trinquart L. Non-opioid analgesics in adults after major surgery: systematic review with network meta-analysis of randomized trials. Br J Anaesth. 2017;118(1):22–31.
14. Barazanchi AWH, MacFater WS, Rahiri JL, Tutone S, Hill AG, Joshi GP, *et al.* Evidence-based management of pain after laparoscopic cholecystectomy: a PROSPECT review update. Br J Anaesth. 2018;121(4):787–803.
15. Zhao T, Shen Z, Sheng S. The efficacy and safety of nefopam for pain relief during laparoscopic cholecystectomy: a meta-analysis. Medicine. 2018;97(10):e0089.
16. Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Li MCT, Page MJ, Welch VA, editors. Cochrane handbook for systematic reviews of interventions. Hoboken, NJ: Wiley-Blackwell; 2019 Sep 23. pp. 205–28.
17. DistillerSR.com. Literature review software. Available from: https://www.distillersr.com/products/distillersr-systematic-review-software
18. Stoll CRT, Izadi S, Fowler S, Green P, Suls J, Colditz GA. The value of a second reviewer for study selection in systematic reviews. Res Synth Methods. 2019;10(4):539–45.
19. Kapfer B, Alfonsi P, Guignard B, Sessler DI, Chauvin M. Nefopam and ketamine comparably enhance postoperative analgesia. Anesth Analg [Internet]. 2005 Jan [cited 2023 Jan 5];100(1):169. Available from: /pmc/articles/PMC1283103/
20. Richebé P, Picard W, Rivat C, Jelacic S, Branchard O, Leproust S, *et al.* Effects of nefopam on early postoperative hyperalgesia after cardiac surgery. J Cardiothorac Vasc Anesth. 2013;27(3):427–35.
21. 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.
22. Son JS, Doo A, Kwon YJ, Han YJ, Ko S. A comparison between ketorolac and nefopam as adjuvant analgesics for postoperative patient-controlled analgesia: a randomized, double-blind, prospective study. Korean J Anesthesiol. 2017;70(6):612–8.
23. Nair A. Nefopam: another pragmatic analgesic in managing chronic neuropathic pain. Indian J Palliat Care [Internet]. 2019 Jul 1 [cited 2023 Jan 5];25(3):482. Available from: /pmc/articles/PMC6659541/
24. 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. 2016;95(20):e3705.
25. Pasutharnchat K, Wichachai W, Buachai R, Yuen Ho K, Hadi Mohamed A. Analgesic efficacy of nefopam for cancer pain: a randomized controlled study. F1000Res. 2020 [cited 2023 Jan 5];9:378. Available from: https://doi.org/10.12688/f1000research.23455.1
26. Lekprasert V, Yapanan L, Ittichaikulthol W, Buachai R, Soisod P, Sophonsritsuk A. Perioperative intravenous patient-controlled analgesic efficacy of morphine with combined nefopam and parecoxib versus parecoxib in gynecologic surgery: a randomized, double-blind study. Anesthesiol Res Pract. 2021;2021:5461890.
27. 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.
28. Yoon S, Lee HB, Na KJ, Park S, Bahk J, Lee HJ. Effect of continuous infusion of intravenous nefopam on postoperative opioid consumption after video-assisted thoracic surgery: a double-blind randomized controlled trial. Pain Physician. 2022;25(6):491–500.
29. Lavand'homme P, Steyaert A. Opioid-free anesthesia opioid side effects: tolerance and hyperalgesia. Best Pract Res Clin Anaesthesiol. 2017;31(4):487–98.
30. Stephan BC, Parsa FD. Avoiding opioids and their harmful side effects in the postoperative patient: exogenous opioids, endogenous endorphins, wellness, mood, and their relation to postoperative pain. Hawaii J Med Public Health. 2016;75(3):63–7.
31. Li Y, Dong H, Tan S, Qian Y, Jin W. Effects of thoracic epidural anesthesia/analgesia on the stress response, pain relief, hospital stay, and treatment costs of patients with esophageal carcinoma undergoing thoracic surgery: a single-center, randomized controlled trial. Medicine. 2019;98(7):e14362.
32. Weber L, Yeomans DC, Tzabazis A. Opioid-induced hyperalgesia in clinical anesthesia practice: what has remained from theoretical concepts and experimental studies?. Curr Opin Anaesthesiol. 2017;30(4):458–65.
33. 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(12):990–2.
34. Moussa MK, Lefevre N, Valentin E, Meyer A, Grimaud O, Bohu Y, *et al.* Dynamic intermittent compression cryotherapy with intravenous nefopam results in faster pain recovery than static compression cryotherapy with oral nefopam: post-anterior cruciate ligament reconstruction. J Exp Orthop. 2023;10(1):72.

How to cite this article:
Bader NA, Al-Ahmad MM, Al Naeem W, Amer MG. Efficacy of nefopam in postoperative pain management: A systematic review of opioid consumption. J Appl Pharm Sci. 2025;15(05):024–039. DOI: 10.7324/JAPS.2025.203223