Journal of Taibah University Medical Sciences (2025) 20(2), 191–200

Taibah University

Journal of Taibah University Medical Sciences

www.sciencedirect.com

Original Article

A meta analysis of efficacy and safety of nefopam for laparoscopic cholecystectomy pain management

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Received 3 September 2024; revised 30 November 2024; accepted 17 February 2025

الملخص

أهداف البحث: الألم الذي يعبر عنه عادة على أنه انزعاج ليس مفهوما غير مألوف لأولئك الذين خضعوا لجراحة استئصال المرارة بالمنظار. في هذا البحث، كان المقصود تقييم فعالية نيفوبام المعروف أيضا باسم عقار تسكين الآلام، باستخدام دواء وهمي في علاج آلام ما بعد الجراحة.

طريقة البحث: تم إجراء البحث في الأدبيات حتى يونيو ٢٠٢٤ باستخدام قواعد البيانات عبر الإنترنت مثل مكتبة "كوكرين"، و "بيميد/ميدلاين"، وويب أوف ساينس. تم استخدام بيانات الأمراض والوفيات جنبا إلى جنب مع نتائج أكثر ذاتية مثل مستويات الألم واستخدام المواد الأفيونية والوظيفة لتحديد جودة الأدلة. تم إجراء التحليل التلوي باستخدام برنامج ريفيو مانيجير.

النتائج: شملت هذه الدراسة ٢٥٤ مشاركا في خمس تجارب عشوائية محكومة. عند فترات زمنية مدتها ٣٠ و ٦٠ دقيقة، لوحظ أن عقار نيفوبام فشل في إظهار تسكين أفضل للألم من الدواء الوهمي. ومع ذلك، فقد قلل من الحاجة إلى مسكنات أخرى والأفيونيات لم يرتبط عقار نيفوبام بشكل كبير بزيادة خطر الغثيان والقيء مقارنة بالدواء الوهمي.

الاستنتاجات: لم يحدث عقار نيفوبام أي فرق في الألم بعد الجراحة، ولكنه كان فعالا في تقليل استهلاك الأفيون بشكل عام والحاجة إلى مسكنات إضافية ولم يزيد من الغثيان والقيء في وحدة العناية بعد الجراحة. يقلل عقار نيفوبام بشكل كبير من استخدام الأفيونات وضرورة التسكين الإضافي، بينما لا يسبب الغثيان والقيء، على الرغم من عدم تأثيره على الألم الذي يشعر به المريض بعد الجراحة. وبالتالي، تشير النتيجة إلى أنه على الرغم من حقيقة أنه ليس أحد الأدوية الرائدة من حيث أغراض تسكين الألم، إلا أنه يشارك بنشاط في تنظيم الألم بعد الجراحة.

الكلمات المفتاحية: نيفوبام؛ الألم بعد الجراحة؛ استئصال المرارة بالمنظار؛ تقليل تناول المواد الأفيونية؛ مسكنات الألم؛ دواء وهمي؛ تجارب عشوائية محكومة

Abstract

Background: Nefopam is a safe analgesic with mild side effects including drowsiness, nausea, vomiting, and sweating. Nevertheless, research is scarce on the impact of nefopam in managing postoperative pain following laparoscopic cholecystectomy (LC), and the advantageous effects of nefopam remain unclear. In this research, the effectiveness of nefopam was compared to placebo for the treatment of postoperative pain following LC.

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Peer review under responsibility of Taibah University.

Production and hosting by Elsevier

 https://doi.org/10.1016/j.jtumed.2025.02.010

Methods: A literature search for randomized controlled trials (RCTs) was performed through June 2024 using online databases including Cochrane Library, PubMed/Medline, and Web of Science. The primary outcome assessed was the quality of postoperative patient pain, and the secondary outcome was side effects that occurred due to the use of nefopam. The Cochrane Risk of Bias (RoB) 2 tool was used to assess the RoB. The meta-analysis was conducted using Review Manager software version 5.4. The risk ratio (RR), mean difference (MD), and standardized mean difference (SMD) were calculated at 95% confidence intervals (CIs).

Results: Five RCTs comprising 254 participants were analyzed. The analysis revealed that compared to placebo, nefopam had no statistically significant effect on the reduction of postoperative pain severity at 30 min (SMD = −0.30, 95% CI: −0.61 to 0.01; P = 0.06) and 60 min (SMD = −0.31, 95% CI: −0.78 to 0.16; P = 0.20). Nefopam reduced the number of opioids taken, as shown in the meta-analysis (SMD = −0.94, 95 CI: −1.35 to −0.53; P < 00001), with minor heterogeneity (P = 0.24, I^2 = 30%). This meta-analysis showed that nefopam lengthened the time to first rescue analgesia (MD = 23.003). and markedly reduced the number patients requiring analgesics compared to baseline (RR = 0.34, 95% CI: 0.22 to 0.54; P < 0.00001).

Conclusion: Nefopam did not cause any difference in total postoperative pain but was effective in reducing overall opioid consumption and the need for supplementary analgesics. It did not increase postoperative nausea and vomiting.

Keywords: Laparoscopic cholecystectomy; Nefopam; Opioid reduction; Postoperative pain

Introduction

Laparoscopic cholecystectomy (LC) is a minimally invasive procedure that is widely preferred because it can reduce mortality rates up to 1% and morbidity rates of 4–8%.[1] The advantages of LC over open cholecystectomy are minimal incision wounds and surgical manipulations, shorter hospital stay, and less pain. LC is a major surgery that has a risk of damage and leakage in the billiard duct (0.25–1.25%), which can cause complications (6–9%) such as stroke, pulmonary embolism, myocardial infarction, kidney and heart failure.[1–5]

Research suggests that 12–60% of postoperative patient readmissions are due to subdiaphragmatic shoulder pain.[2,6] A study on treadmill knee surgery found that patients required oral pain medication for a period ranging from 1 day after surgery to 22 ± 0.03 days.[1] In addition to opioids, common pain management options include nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2)-specific inhibitors, and local anesthetic infusion at the operative site. The numerous side effects of opioids restrict their use to emergency conditions.[6]

Nefopam is a centrally acting analgesic that is non-opioid and non-steroidal, primarily used to manage postoperative pain as part of a multimodal analgesia strategy. Unlike traditional analgesics, nefopam does not target opioid receptors; instead, it works by inhibiting the reuptake of neurotransmitters such as serotonin, norepinephrine, and dopamine. This action increases the availability of these neurotransmitters in the synaptic cleft, enhancing central pain through modulation pathway. Due to its mechanism, nefopam proves effective for both acute and chronic pain relief.[4,7,8] Research indicates that its incorporation into multimodal analgesia during lung resection surgeries can lead to reduced reliance on opioids.[9] It has been determined that this treatment is effective for both acute and chronic pain in medical settings. However, its standalone postoperative analgesic role has not yet been widely recognized.[7,10] It is a safe analgesic with mild adaptable side effects including drowsiness, nausea, vomiting, and sweating.[11] To assess the efficacy and safety of nefopam in postoperative pain management, we conducted a meta-analysis of randomized controlled trials (RCTs) that focused on its use in LC surgery. This analysis clarified nefopam's potential as a viable option for postoperative analgesia.

Materials and methods

This systematic review and meta-analysis adhered to the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).[12,13] This study is registered in PROSPERO under reference number, CRD42024567496.

Search strategy

Until June 30, 2024, all databases such as Cochrane Library, PubMed, Web of Science, and Scopus were searched for studies that evaluated the effectiveness of nefopam and placebo in reducing postoperative pain after the LC. Boolean operators were employed in the search expression their possible synonyms, "nefopam" OR "Nefopam Hydrochloride" OR "Fenazoxine OR Acupan OR Ajan" and "Cholecystectomy." Specifically, we considered whole papers and compared them with the criteria for inclusion and exclusion.

Inclusion criteria and selection

Population: Studies in which patients with cholecystitis were included for LC. Intervention: Intraoperative nefopam was given to the intervention group to reduce postoperative pain. Comparator: Patients who did not receive nefopam or received normal saline intraoperatively. Outcomes: Primary outcomes included pain measurements, postoperative opioids, time of first rescue analgesia postoperatively, and number of patients requiring analgesia postoperatively.

Secondary outcomes included complications such as nausea and vomiting. Study design: RCTs.

Data extraction

For every published article, the data points including the author, year of publication, place, type of study, population type, and sample size were extracted. Additional data included the length of the study, the way the results are going to be evaluated, method of evaluation, length of surgery, length of anesthesia, dosage used, and side effects. Features of the patient included age, sex, height, weight, body mass index, groups that received treatments, and the measurements of the results. Primary outcomes included pain measurements, postoperative opioids, time of first rescue analgesia, and number of patients requiring analgesia. The secondary outcomes included complications such as nausea and vomiting.

Risk of bias assessment

Organization of the clinical trials included in this analysis was done according to their paper, and the Cochrane Risk of Bias (RoB) 2 tool was used to assess the RoB in the RCTs, including interventional studies.[14] This tool measures several factors based on the potential bias source: results reporting, allocation concealment, participants and staff blinding, outcome assessor blinding, missing outcome details, and other sources of bias. Two writers assessed each domain separately and assigned RoB as high, low, and unclear. We used grade assessment to investigate the certainty of evidence among the included outcomes.

Statistical analyses

A meta-analysis was performed with Review Manager software (RevMan v.5.4) when at least three trials included the available evidence for the specified outcomes.[15] In the case of continuous outcomes, the mean difference (MD) with the 95% confidence intervals (CIs) of the estimates were applied to calculate the effect size. Cohen's d was used instead of specific scales, and when required based on the context, the standardized mean difference (SMD) was employed. Where outcomes were categorized into two groups, the number of events and the total number of individuals in each group were summed and used in estimation of the risk ratio (RR) together with the 95% CI. When the P-value is less than 0, the hypothesis is valid meaning that there is sufficient evidence to reject the null hypothesis. When the P-value is less than 0.05, the level of significance is considered to have been achieved. Instead of a change in baseline numbers, the final numbers were extracted. Where possible, we standardized figures to a unit where they were expressed in different units. In the cases when it was impossible to take measurements manually, data were extracted from the figures using the Plot Digitizer web-based tool. In an attempt to control for study heterogeneity, a random-effects model (inverse variance) instead of a fixed-effects model was used to calculate the effect estimate. Heterogeneity was evaluated based on the chi-square test $P < 0.1$ and $I^2 > 40\%$. However, to increase the efficiency of the analysis in the case of a few trials, the I^2 value was used more frequently. Sensitivity analysis using the leave-one-out method was conducted to identify the studies that caused heterogeneity among the outcomes. We conducted trial sequential analysis (TSA) to account for the small sample size of the included outcomes using R programming. TSA is a cumulative meta-analysis technique developed to account for both α and β errors, helping to determine when the effect size is sufficiently large that additional studies are unlikely to change the result.[16,17] Publication bias using funnel plots could not be conducted due to the small number of studies in each outcome.

Results

Study selection

An initial search of the literature databases, including PubMed, Cochrane Central, Scopus, and Web of Science, returned 55 papers that may be related to the study. A total of 19 records were duplicates; thus, they were deleted using Endnote. This left us with 36 entries, of which only 11 met the eligibility criteria for the topic of this research. The last process of scoring was done by reading through the whole text; six items were deleted for various reasons such as repetition of information in another part of the text. Therefore, although the meta-analysis comprised four publications, the qualitative synthesis involved five publications (Al-Awwady 2020,[18] Choi 2016,[19] Kim 2017,[7] Lee 2013,[8] Zeeni 2023[2]). Figure 1 illustrates the search process and the number of studies that were included and excluded during the process.

Study characteristics

All studies in the meta-analysis were published between 2013 and 2023. All five included studies are RCTs and evaluated the effectiveness of nefopam for pain relief after LC. The five included studies in the qualitative synthesis compared nefopam against placebo. The sample size ranged from 18 to 45 participants, and there was concomitant use of opioids or other analgesics for uncontrolled pain after surgery. The overall population was 254 participants who underwent LC. A summary of the included studies and baseline characteristics of patients are shown in Supplementary Tables 1 and 2

Risk of bias assessment

In determining the aspects of bias in all seven domains, the RCTs were rated using the RoB 2 tool. It is believed that little to no prejudice was detected in the analyses of Choi 2016, Kim 2017, Zeeni 2023, and Al-Awwady 2020.Due to failure in the process of randomization and allocation, and high level of blinding risk, the Lee 2013 study was classified as high RoB. The graph showing the RoB is presented in Figure 2, which presents an overall summary of that risk.

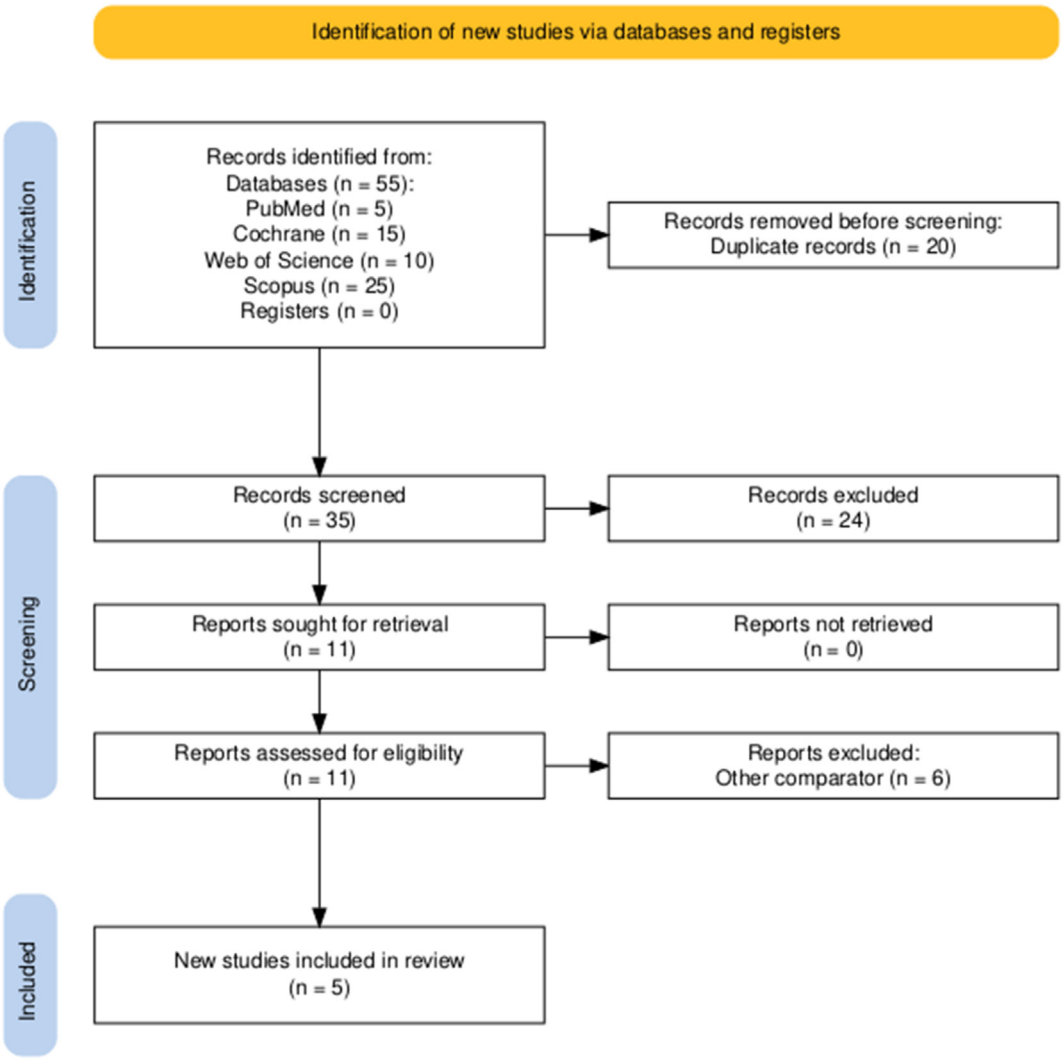

Figure 1: PRISMA flow diagram.

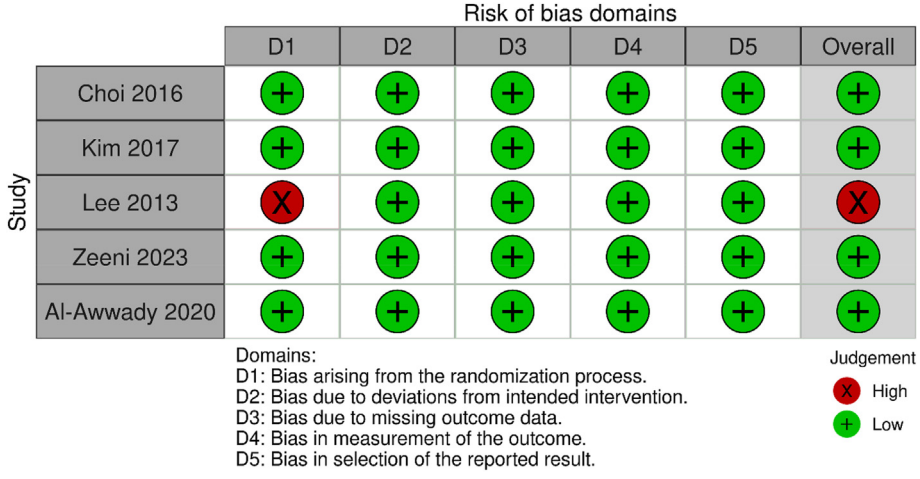

Figure 2: Risk of bias assessment of the included studies.

Grading assessment

According to grading assessment of the primary outcomes, the level of certainty was high in one outcome, moderate in two outcomes, and low in one outcome (Supplementary Table 3). High level is associated with strong recommendations, moderate level is associated with recommendations with caution, and low level is associated with weak recommendations.

Efficacy outcomes

Postoperative pain at 30 and 60 min

In the present study, the pain-relieving or analgesic property of nefopam was regarded as the main measure. Pain after surgery was reported in four studies, and it was measured by two different sets of measurements. Zeeni 2023 employed the Numerical Rating Scale (NRS) to measure pain intensity, whereas Choi 2016, Kim 2017, and Lee 2013 employed the Visual Analog Scale (VAS) to measure the pain intensity. The forest plots revealed that nefopam has no statistically significant effect on the reduction of postoperative 30- and 60-min pain severity compared to placebo (SMD = −0.30, 95% CI: −0.61 to 0.01; P = 0.06) and (SMD = −0.31, 95% CI: −0.78 to 0.16; P = 0.20) at 30 and 60 min, respectively (Figure 3). Due to moderate heterogeneity in postoperative pain at 30 min (P = 0.15, I^2 = 41%) and marked heterogeneity at 60 min (P = 0.004, I^2 = 74%), we conducted sensitivity analysis and found that the heterogeneity was resolved by removing Zeeni 2023.

Postoperative opioid consumption

One of the measurement tools used in three of the included studies was postoperative opioid use, another relevant goal. The meta-analysis showed that nefopam reduced the number of opioids taken (SMD = −0.94, 95% CI: −1.35 to −0.53; P < 00001), with minor heterogeneity (P = 0.24 I^2 = 30%) (Figure 4).

Time to first rescue analgesics

This meta-analysis showed that nefopam lengthened the time to first rescue analgesia (MD = 23.003). Overall the meta-analysis of the two pools of study showed considerable heterogeneity (P = 0.05, I^2 = 73%), which could not be alleviated by sensitivity or subgroup analysis (Figure 5).

Number of patients requiring analgesics

The frequency of patient analgesic consumption was assessed in three different trials, namely, Choi, Kim, and Zeeni. The analysis showed that nefopam dramatically reduced the number patients requiring analgesics compared to baseline (RR = 0.34, 95% CI: 0.22 to 0.54; P < 0.00001). The meta-analysis of both the studies demonstrated the homogeneity (P = 0.67, I^2 = 0%) (Figure 6).

Safety outcomes

Choi 2016 and Zeeni 2023 both analyzed pruritus and tachycardia in their studies. On the other hand, Lee 2013 focused on nausea, vomiting, and the necessity of rescue antiemetic at two doses (20 and 40 μg).

Nausea

We found no significant difference in nausea data when comparing nefopam to placebo (RR = 0.59) (Supplementary Fig. 1). The pooled research was heterogonous (P = 0.02, I^2 = 74%); hence, neither subgroup nor sensitivity analysis provided a solution.

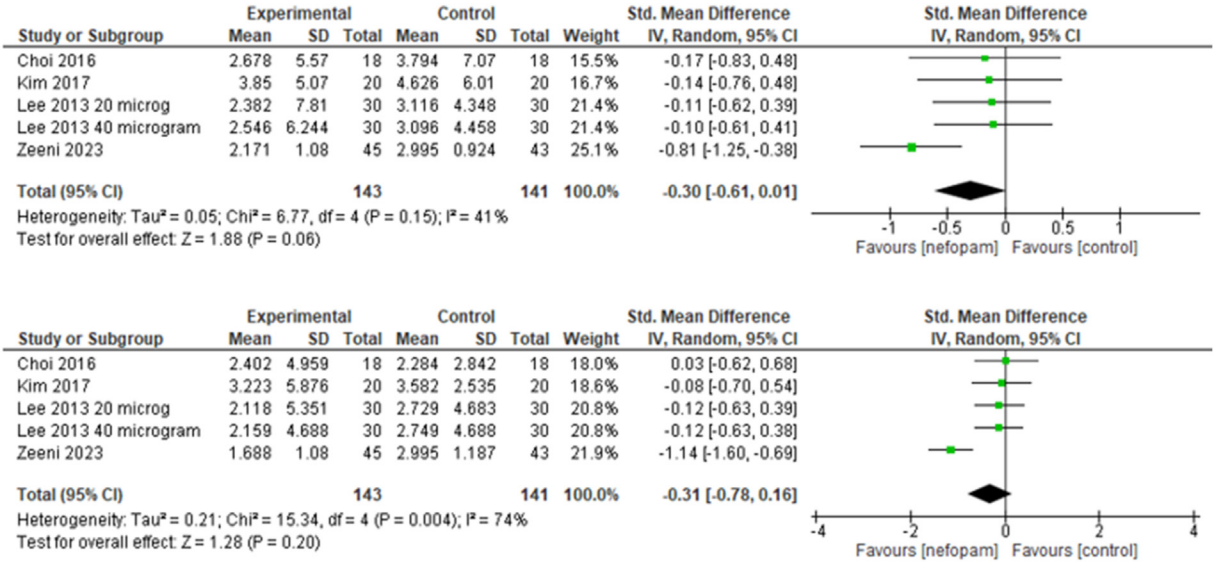

Figure 3: Forest plot of pain score at 30 and 60 min outcome.

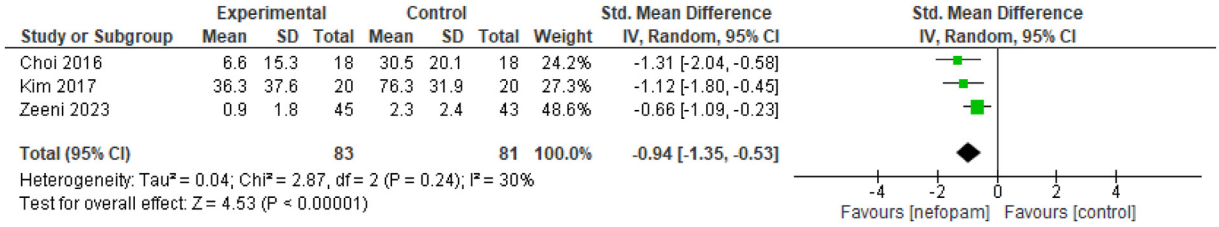

Figure 4: Forest plot of opioid consumption outcome.

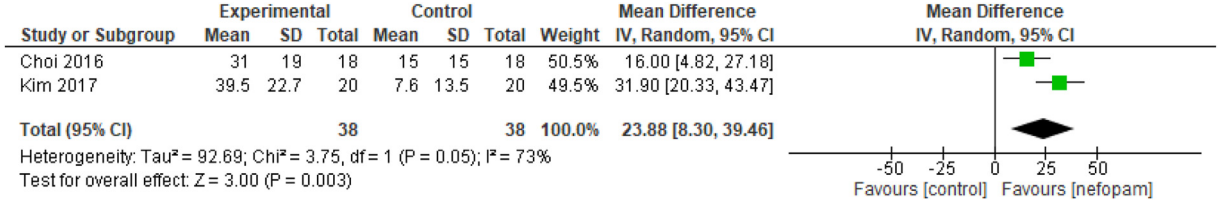

Figure 5: Forest plot of time to first rescue analgesia outcome.

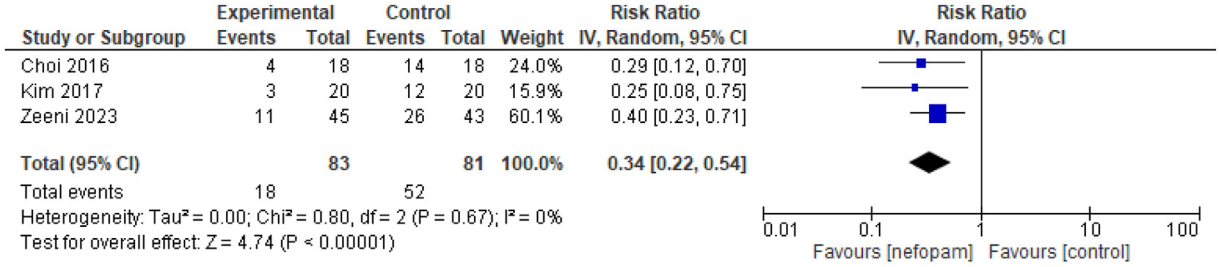

Figure 6: Forest plot of the number of patients requiring analgesia outcome.

Vomiting

In cases of vomiting, the authors found no significant difference in the effect of nefopam and placebo (P = 0.58; 95% CI: 0.42) (Supplementary Fig. 2). Collectively, the results of the studies were in alignment with each other (P = 0.65, I^2 = 0%).

Rescue antiemetic

When separate data were obtained for the patients where rescue antiemetics were needed, the meta-analysis did not find any significant difference between nefopam and placebo (RR = 0.74, 95% CI: 0.52) (Supplementary Fig. 3). Due to the characteristics of the studies combined in the meta-analysis, including trials of different origins and with different methodologies (heterogonous), we could not perform subgroup analysis or sensitivity analysis due to the great variability of the data obtained (P = 0.05, I^2 = 66%).

Pruritus

Compared with placebo, nefopam was not statistically significant for pruritus in terms of RR (RR = 0.99, 95% CI: 0.11 to 9.23; P = 0.99). This indicates that the forest plots in the pooled research consisted of homogeneous datasets (P = 0.32, I^2 = 0%) (Supplementary Fig. 4).

Tachycardia

In cases where PAGE ＼# "'Page: '#'" vomiting, there was a nonsignificant difference if nefopam was compared to the placebo (RR = 2.34). Thus, the forest plots of comparing the pooled research were similar (P = 0.98, I^2 = 0%) (Supplementary Fig. 5).

Trail sequential analysis

Postoperative pain at 30 and 60 min

The TSA for postoperative pain scores at 30 min showed a significant MD of −0.8187 (95% CI: −1.2249 to −0.4124; P < 0.0001), indicating that the intervention effectively reduced pain. While individual studies like Choi 2016 (P = 0.5988), Kim 2017 (P = 0.4994), Lee 2013 (20 µg, P = 0.4196), and Lee 2013 (40 µg, P = 0.3778) did not show significant effects, the significant finding from Zeeni 2023 (P < 0.0001) contributed to the overall effect. With an I^2 of 0.0%, there was no observed heterogeneity among the studies, reinforcing the conclusion that the intervention was

likely effective in reducing postoperative pain scores at 30 min (Supplementary Fig. 6). The data analysis across five studies showed mostly small to medium negative effect sizes, with Zeeni 2023 exhibiting a much larger negative effect. The Cohen's d values ranged from −0.175 in Choi 2016 to −1.152 in Zeeni 2023, indicating that the experimental groups generally performed worse than the control groups, although the effect sizes were small in most studies. The RIS vary, with Zeeni 2023 needing only 6.79 participants, while other studies like Lee 2013[8] (40 μg) required a larger sample size of 442.40 for adequate power. The cumulative sample size increased progressively, reaching 284 after including all studies. The cumulative Z-scores also showed a growing negative trend, from −0.180 after Choi 2016 to −1.373 after Zeeni 2023, driven by the larger negative effect in the latter study. These results suggested a generally negative trend, although the effect was more pronounced in Zeeni 2023, which significantly impacted the cumulative results.

The TSA for postoperative pain scores at 60 min indicated that the pooled MD was −0.9792, with a 95% CI ranging from −1.3355 to −0.6228, suggesting a significant reduction in pain scores associated with the intervention. The P-value for the overall pooled estimate was <0.0001, indicating strong statistical significance. Individual studies such as Zeeni 2023 contributed notably to this effect, whereas others showed less pronounced changes. Importantly, the analysis indicated moderate heterogeneity ($I^2 = 40.0\%$), particularly due to variability in the results of Zeeni 2023. These findings indicate that the intervention was likely effective in alleviating postoperative pain at this time point; however, caution should be exercised due to the observed variability among studies (Supplementary Fig. 7). The TSA results for the studies Choi 2016, Kim 2017, Lee 2013 20 μg, Lee 2013 40 μg, and Zeeni 2023 revealed several insights. The effect sizes for the studies were generally small or negative: Choi 2016 (0.029), Kim 2017 (−0.079), Lee 2013 20 μg (−0.122), Lee 2013 40 μg (−0.126), and Zeeni 2023 (−1.152), with Zeeni 2023 showing a substantial negative effect in favor of the control group. The RIS indicated the sample sizes needed to detect a significant effect: Choi 2016 required 18,415 participants, Kim 2017 needed 2,494, Lee 2013 20 μg required 1,063, Lee 2013 40 μg needed 991, and Zeeni 2023 needed only 12 participants, reflecting the large effect size in that study. The cumulative sample sizes across the studies were 36, 76, 136, 196, and 284, respectively, growing as more studies were included. However, the cumulative Z-scores were all negative and below the threshold for statistical significance, with values of 0.088, −0.163, −0.634, −1.121, and −6.517, indicating that no significant effect was detected when considering the data cumulatively. Despite the growing sample sizes, the results suggested insufficient evidence for a statistically significant effect.

Postoperative opioid consumption

The TSA results for opioid consumption indicated significant reductions across three studies: Choi 2016 (MD = −23.90), Kim 2017 (MD = −27.53), and Zeeni 2023 (MD = −1.59), with a pooled estimate of −1.59. CIs confirmed that these reductions were statistically significant: Choi 2016 (−35.57; −12.23), Kim 2017 (−37.80; −17.27), and Zeeni 2023 (−2.48; −0.71). All studies showed strong P-values ($P < 0.0001$ for Choi and Kim, and $P < 0.0004$ for Zeeni 2023), indicating robust evidence of the intervention's effectiveness. However, there was considerable heterogeneity among the studies, particularly in Zeeni 2023 ($I^2 = 92.4\%$), suggesting variability in effects. Overall, the findings highlight that the interventions effectively reduced opioid consumption in postoperative patients, but further investigation may be needed to understand the sources of variation (Supplementary Fig. 8). The TSA of the studies showed that the cumulative effect sizes were negative across all studies, indicating that the experimental group performed worse than the control group. The effect sizes were −1.338 for Choi 2016, −1.243 for Kim 2017, and −1.048 for Zeeni 2023, with the effect size decreasing as more data was added. The RIS indicated that larger sample sizes were necessary for conclusive results, particularly for the Kim 2017 study, which required 7249.86 participants, compared to Zeeni 2023, which had a smaller RIS of 81.09. The cumulative sample sizes were 36, 76, and 164, respectively, for the studies in the order of their appearance. Despite increasing sample sizes, the cumulative Z-scores remained close to 0, with values of −0.225, −0.198, and −0.251 for Choi 2016, Kim 2017, and Zeeni 2023, respectively, suggesting that statistical significance had not been reached. This indicates that additional data or studies may be needed to confirm the findings and achieve a valid conclusion.

Discussion

This systematic review and meta-analysis evaluated the efficacy and safety of nefopam compared with placebo for postoperative pain relief. Comparison of the change in VAS score of pain intensity at 30 and 60 min postoperatively was not statistically significant. The pooled results also indicated the fact that nefopam did not offer a clinically significant improvement in pain relief that is required for immediate postoperative pain in contrast to the reported differences in the measures of pain score used throughout the trials included in the meta-analysis such as the VAS and the NRS.

These findings challenge the notion of nefopam as an effective first-line analgesic for acute postoperative pain. While the absence of a significant difference might be attributed to factors such as study design, patient population, or dosage, the consistent lack of effect across multiple studies raises concerns about the drug's analgesic efficacy in this setting. Further research is warranted to explore the potential benefits of nefopam in specific patient populations or when combined with other analgesic modalities. The grading assessment showed that the effect of nefopam on postoperative opioid consumption was of a high level of certainty, which was associated with strong recommendation among clinicians; postoperative pain and number of patients requiring analgesia were of moderate level of certainty so recommendations were made with caution; and time of first rescue analgesia was of low level so weak recommendations were made, often accompanied by qualifiers that emphasized the need for careful consideration of individual cases.

The examination outcomes, which included data collected at 30 and 60 min after surgery, were obtained from several studies on the assessment of analgesic drugs. However, this early evaluation may not be a true measure of the drugs' capacities for producing analgesia because the results could have been complicated by the residual effects of anesthesia. Alternatively, we postulate that the degree of pain at certain subsequent time points may be a better predictor of the effectiveness of analgesics, for example at postoperative hour 6 or 12. Later time points may minimize the interference of the effects of the analgesic medication with the effects of the given anesthesia.

The effectiveness of nefopam as an analgesic has been assessed in numerous clinical studies.[10,20–23] With supraspinal and spinal sites of action, nefopam is a strong non-narcotic analgesic,[24,25] which regulates descending serotonergic pain and inhibits the uptake of noradrenaline and 5-hydroxytryptamine.[26] Nefopam relieved postoperative pain more effectively than placebo. The manufacturer suggests an intravenous injection of 20 mg every 4–6 h; however, the rationale behind this recommendation is not evident, and the median effective dose has never been ascertained.[27] Nefopam injections after surgery are known to enhance postoperative analgesia and decrease morphine usage.[28,29] Previous studies have reported side effects such as nausea, vomiting, malaise, excessive sweating, sleeplessness, palpitations, tachycardia, and vertigo, which are frequently attributed to the medication's anticholinergic effects.[30,31] When opioids are administered, common side effects include constipation, physical dependence, respiratory depression, nausea, vomiting, dizziness, and sedation. Clinical concerns including physical dependence and addiction may make it difficult to prescribe appropriately, which could lead to insufficient pain management.[32]

In this study, nefopam was proven to be useful in decreasing the consumption of opioids in the postoperative period and deferring the need for early rescue analgesics. These observations indicate that nefopam might be useful in sparing opioids and thus postponing the use of other therapies for controlling postoperative pain. As the study based on interspecific variability pointed out moderate to significant variability in some of the outcomes, including the time to the first rescue analgesia, most of the subgroup or sensitivity analyses could not account for huge differences across the research results.

Measurement of other safety characteristics, including rescue antiemetics, was also performed in addition to such safety outcomes as nausea and vomiting. In the meta-analysis of the adverse events, there were no significant differences noted between nefopam and placebo. Of the two effects, pruritus and tachycardia, the results of the nefopam and placebo do not differ significantly, and the findings were consistent across studies.

Nefopam demonstrated potential as a postoperative analgesic with a focus on opioid reduction. While it did not show immediate superiority to placebo in relieving acute pain, its ability to delay the need for additional analgesia is promising. This suggests that nefopam might be more effective in managing prolonged postoperative pain rather than providing rapid, short-term relief. Moreover, the drug appears to have a comparable safety profile to placebo, indicating a potentially favorable benefit-risk ratio.

However, further studies are required to elucidate theoretically the role of nefopam in treating the postoperative pain as on the basis of these findings. To understand how nefopam can benefit patients, it is crucial to determine the optimal doses and when to administer the drug, in addition to the patient type. The position of nefopam as a multimodal analgesic concept should also be defined by the head-to-head comparisons with other non-opioid analgesics. Therefore, the optimal utilization of nefopam will require an understanding of the drug's safety and efficacy.

In accordance with the present results, nefopam was shown in earlier research to lower postoperative pain levels and morphine intake by up to 13 mg in major surgeries.[33–35] Another trial, however, found that patients who underwent open spine surgery and received intravenous nefopam before the skin incision and prior to the conclusion of the procedure, experienced comparable levels of morphine intake and postoperative pain to those in the placebo group.[36]

Limitations

At present, there few papers that incorporate different techniques, so there is less scope for conducting this meta-analysis. Therefore, there are issues of generalizing these findings, as will be discussed later on. Thus, it is important to stress that further investigations with larger groups of participants are needed to strengthen the evidence for the investigated effects. Future RCTs with greater sample sizes are needed for studies of a similar nature. Sharing of certain type of proof figures was constrained by the small sample sizes, analyses that could have been helpful in identifying subgroup leave-one-out, and the regularity or dependability of the data and the publication bias.

Conclusions

Nefopam was only effective in mildly reducing the magnitude of acute postoperative pain. However, with regards to the claim that it has an analgesic effect after surgical operations, the analysis showed that the pain reduction was not much greater than placebo at 30 or 60 min after surgery. The meta-analysis was consistent in showing that patients who were prescribed nefopam received fewer opioids and required less supplemental analgesia – the primary one at that. Here, the opioid-sparing impact of the single-shot nerve block was only moderately influenced by differences between the trials. Nefopam did not increase the incidence of any side effect, such as nausea, vomiting, or need for an antiemetic, compared with placebo and standard care.

From these findings, it appears that although nefopam may not be ideal for the initial treatment of surgical pain, it could be useful as an add-on to reduce the opioid requirement in the postoperative period. Although it produced maximal impact in such an environment, additional studies may be needed to elucidate the optimal patient population, time, and dosage.

Source of funding

This work was supported by the Deanship of Scientific Research, Vice Presidency for Graduate Studies and Scientific Research, King Faisal University, KSA (Grant No. KFU250915).

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethical approval

Not applicable as this review article involves already published articles and there is no ethical issue.

Author contributions

All authors substantially contributed to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work; drafting the manuscript or revising it critically for important intellectual content; and final approval of this version to be published.

Acknowledgments

The authors acknowledge the Deanship of Scientific Research at King Faisal University for obtaining financial support for research, authorship, and the publication of research under Research Proposal Number KFU250915.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtumed.2025.02.010.

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How to cite this article: Aleid AM, Barnawi MI, Alshamoosi MS, Aldanyowi SN, Al Mutair AS. A meta analysis of efficacy and safety of nefopam for laparoscopic cholecystectomy pain management. J Taibah Univ Med Sc 2025;20(2):191–200.