

The efficacy and safety of nefopam for pain relief during laparoscopic cholecystectomy

A meta-analysis

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Abstract

Background: Pain control after laparoscopic cholecystectomy (LC) has become an important topic. We performed a meta-analysis of randomized controlled trials (RCTs) to evaluate the efficacy and safety of nefopam for pain management after LC.

Methods: PubMed, Medline, Embase, ScienceDirect, and the Cochrane Library were searched up to November 2017 for comparative articles involving nefopam and placebo for reducing postoperative pain after LC. Primary outcomes were postoperative pain scores and opioid consumption. Secondary outcomes were length of hospital stay, opioid-related adverse effects, and postoperative complications. We assessed statistical heterogeneity for each RCT by using a standard Chi^2 test and the I^2 statistic. The meta-analysis was undertaken using Stata 12.0.

Results: A total of 215 patients were analyzed across 4 RCTs. We found that there were significant differences between nefopam and placebo groups regarding the postoperative pain scores and opioid requirements at 6, 12, and 24 hours. Moreover, there was a decreased risk of opioid-related adverse effects in the nefopam groups. No significant differences were identified in terms of the incidence of postoperative complications.

Conclusion: Intravenous nefopam infusion resulted in significant reduction in postoperative pain scores and opioid requirements while decreasing opioid-related adverse effects. Additionally, no increased risk of venous thromboembolism was found. The current evidence suggests that more RCTs will be needed in further investigations.

Abbreviations: DVT = deep venous thrombosis, LC = laparoscopic cholecystectomy, PE = pulmonary embolism, RCT = randomized controlled trials, VAS = visual analog scale.

Keywords: laparoscopic cholecystectomy, meta-analysis, nefopam, pain management

1. Introduction

Laparoscopic cholecystectomy (LC) is a minimally invasive surgical procedure, which has become the gold standard for the treatment of symptomatic cholelithiasis and acute cholecystitis.^[1] Although minimal incision enhances early recovery and decreases postoperative complications, patients often complain of moderate to severe pain. It is reported that there are approximately 750,000 cholecystectomies performed annually in the United States.^[2] Thus, pain control after LC has become an important social issue. Various strategies have been introduced to treat postoperative pain and the optimal analgesia regime remains

unresolved. Multimodal analgesia is recommended for postoperative management after LC.^[3]

Nefopam is a centrally acting nonopioid analgesic belonging to the benzoxazocine class that controls postoperative pain.^[4] Fundamental research has shown that it inhibits reuptake of serotonin, norepinephrine, and dopamine. Nefopam was first introduced in the 1970s^[5] and is now widely used in the fields of surgical oncology, orthopedics, gynaecology, and obstetrics. Na et al^[6] demonstrated that nefopam was helpful in reducing acute postoperative pain, which reduced use of rescue analgesic drugs after breast cancer surgery. Hwang et al^[7] showed that nefopam was associated with a lower incidence of nausea after gynecologic surgery and it may be an effective analgesic drug for the opioid-based patient-controlled analgesia.

However, only a small number of articles have focused on nefopam for pain control after LC, and the beneficial effect remains controversial. Based on the published randomized controlled trials (RCTs), we performed a meta-analysis to evaluate the efficacy and safety of nefopam for pain control after LC. The objective of the meta-analysis was to determine whether nefopam is associated with the following: less postoperative pain, less opioid consumption, shorter length of hospital stay, and fewer opioid-related adverse effects and postoperative complications compared to the control groups.

2. Material and methods

This study was reported according with the guideline of PRISMA statement. Ethical approval was not required because this was a meta-analysis of published articles.

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TZ and ZS equally contributed to this study.

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2.1. Search strategies

PubMed, Medline, Embase, ScienceDirect, and the Cochrane Library were searched up to November 2017 for comparative articles involving nefopam and placebo for reducing postoperative pain after LC. The following search terms were used in combination with Boolean operators AND or OR: “Laparoscopic cholecystectomy,” “nefopam,” and “pain OR analgesia.” We made no restrictions on the publication language. The reference lists of all the full-text articles were examined to identify additional potential included studies. Two reviewers (TCZ and ZS) independently scanned the titles and abstracts of all the relevant literature. Subsequently, the full studies were scanned to determine whether articles fit the inclusion and exclusion criteria. Disagreements were resolved by consulting an additional reviewer (SHS).

2.2. Inclusion criteria and study selection

Participants: Published articles enrolling patients with a diagnosis of symptomatic cholelithiasis and acute cholecystitis who prepared for LC; **Interventions:** The intervention groups received intravenous nefopam for postoperative pain management; **Comparisons:** The control groups received normal saline or nothing; **Outcomes:** Visual analog scale (VAS) scores, narcotic consumption, length of hospital stay, opioid-related adverse effects, and postoperative complications; **Study design:** Only RCTs were included in the meta-analysis. Studies would be excluded for non-RCTs, letters, comments, editorials, and other articles with incomplete data.

2.3. Data extraction

Each of the included publication was examined by 2 reviewers and key data were extracted including first author's name, publication year, study design, sample size, age, gender, intervention of each groups, duration of follow-up, and outcomes measures. Primary outcomes were VAS scores and opioid consumption. Secondary outcomes were length of hospital stay, opioid-related adverse effects, and postoperative complications. Corresponding authors were consulted to obtain incomplete outcome data.

2.4. Quality assessment

A quality assessment of each RCT was performed according to the Cochrane Handbook for Systematic Reviews of Interventions. Two authors independently evaluated the risk of bias of the included RCTs based on the following items: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other sources of bias.

A reviewer author was the adjudicator when no consensus can be reached.

The evidence grade was assessed using the guidelines of the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation)^[8] working group including the following items: risk of bias, inconsistency, indirectness, imprecision and publication bias. The recommendation level of evidence was classified into the following categories: high, which meant that further research is unlikely to change confidence in the effect estimate; moderate, which meant that further research is likely to significantly change confidence in the effect estimate but may change the estimate; low, which meant that further research is likely to significantly change confidence in the effect estimate and

to change the estimate; and very low, which meant that any effect estimate is uncertain. GRADE pro Version 3.6 software was used for the evidence synthesis.

2.5. Data analysis

The meta-analysis was undertaken using Stata 12.0 (<http://www.stata.com>). After extracting the data from the included RCTs, the results were expressed by mean and standard deviation. Then, we assessed statistical heterogeneity for each RCT with the use of a standard Chi² test and the I² statistic. When there was statistical evidence of heterogeneity (I² > 50%, P < 0.05), a random-effects model was adopted; otherwise, a fixed-effects model was used. Dichotomous outcomes were expressed as risk differences (RDs) with 95% confidence intervals (CIs). For continuous outcomes, weighted mean differences (WMDs) and 95% CIs were calculated. Because no more than 10 studies were included in the meta-analysis, publication bias was not detected.

3. Results

3.1. Search result

A total of 215 relevant articles were identified according to the initial search. Around 206 studies were excluded for duplication. After reading the titles and abstracts, 3 articles were excluded for case reports and reviews, 2 articles were excluded for non-RCT. No additional articles were obtained after the reference review. Finally, 4 RCTs^[9–12] which published between 2013 and 2017 were included in the present meta-analysis. These studies involved 99 participants in the nefopam groups and 99 participants in the control groups. The search process was proceed as presented in Figure 1.

3.2. Study characteristics

The sample size ranged from 36 to 60 and average age ranges from 41 to 50 years old. In these studies, the intervention groups received intravenous nefopam for pain management and the control groups received placebo or nothing. Concomitant pain control included intravenous opioid or patient-controlled analgesia. Duration of follow-up ranges from 1 to 3 months. The characteristics of the included articles were shown in Table 1.

3.3. Risk of bias

Seven aspects of the RCTs related to the risk of bias were assessed, following the instructions in the Cochrane Handbook for Systematic Reviews of Interventions (Fig. 2) Randomization was performed in all RCTs and 3 of them^[10–12] mentioned that the list of random numbers were generated from computers. Only one article^[11] used sealed envelopes for allocation concealment. All articles reported blinding to the surgeons, participants, or assessors. Low risk of bias due to incomplete outcome data and selective outcome reporting were detected. None of the RCTs reported whether an “intention-to treat” analysis was conducted.

3.4. Primary outcomes

3.4.1. Postoperative VAS at 6 hours. Four studies^[9–12] reported VAS at 6 hours after LC. There was no significant heterogeneity among the studies ($\chi^2=1.65$, $df=3$, $I^2=0.0\%$, $P=.648$) and a fixed-effects model was adopted. The pooled results of the studies showed that there was significant difference

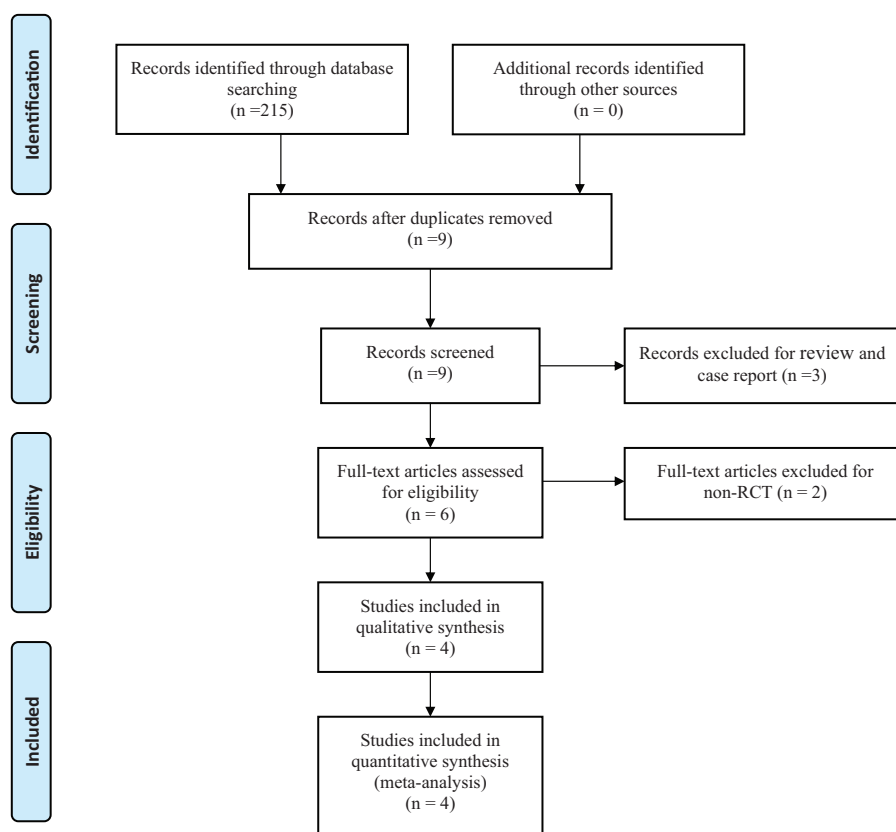


Figure 1. Search results and the selection procedure. RCT=randomized controlled trial.

between nefopam versus controls in VAS at 6 hours (WMD = -0.736, 95% CI: -1.296 to -0.176, P = .010; Fig. 3).

3.4.2. Postoperative VAS at 12 hours. Four studies^[9-12] showed the outcome of postoperative VAS at 12 hours after LC. There was no significant heterogeneity between studies ($\chi^2 = 3.45$, $df = 3$, $I^2 = 13.1\%$, $P = .327$). The pooled results of the studies showed that there was significant difference between the groups regarding to postoperative VAS at 12 hours (WMD = -0.665, 95% CI: -1.275 to -0.054, $P = .033$; Fig. 4).

3.4.3. Postoperative VAS at 24 hours. Four studies^[9-12] including 198 patients, tested the effect of nefopam in postoperative VAS at 24 hours after LC. A fixed-effects model

was performed because no significant heterogeneity was found among the studies ($\chi^2 = 1.66$, $df = 3$, $I^2 = 0.0\%$, $P = .646$). There was significant difference in terms of postoperative VAS at 24 hours between 2 groups (WMD = -0.757, 95% CI: -1.334 to -0.179, $P = .010$; Fig. 5).

3.4.4. Postoperative opioid requirements at 6 hours. Details regarding opioid requirements at 6 hours was available in 4 RCTs.^[9-12] There was no significant heterogeneity ($\chi^2 = 0.32$, $df = 3$, $I^2 = 0\%$, $P = .956$), therefore, a fixed-effects model was used. The overall pooled results indicated that compared with placebo, nefopam could significantly reduce postoperative opioid requirement (WMD = -3.800, 95% CI: -6.877 to -0.723, $P = .015$; Fig. 6).

Table 1
Trials characteristics.

Author	Study design	Surgical type	Sample size (N/C)	Mean age (N/C)	Female patient (N/C)	Nefopam group	Control group	Concomitant pain control after LC in nefopam and control group	Follow-up
Lee et al ^[9]	RCT	LC	30/30	50/48	15/17	Intravenous 40 mg nefopam	Normal saline	Patient-controlled analgesia	2 months
Lee et al ^[10]	RCT	LC	31/31	42/48	16/15	Intravenous nefopam 30 mg mixed with normal saline 500 ml	Normal saline	Intravenous opioid	3 months
Choi et al ^[11]	RCT	LC	18/18	49/49	10/9	Intravenous nefopam 0.3 mg/kg at the induction of anesthesia followed by a continuous infusion of 0.065 mg/kg/h	None	Intravenous opioid	1 month
Kim et al ^[12]	RCT	LC	20/20	41/48	14/14	Intravenous nefopam 0.3mg/kg was given, followed by continuous infusion (65 μg/kg/h)	Normal saline	Intravenous opioid	2 months

C=control, LC=laparoscopic cholecystectomy, N=nefopam, RCT=randomized controlled trial.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Choi, 2016	+	+	+	+	+	?	?
Ki, 2014	+	?	+	+	+	?	?
Kim, 2017	+	?	+	+	+	?	?
Lee, 2013	?	?	+	+	+	?	?

Figure 2. Methodological quality of the randomized controlled trials.

3.4.5. Postoperative opioid requirements at 12 hours. Postoperative opioid requirements at 12 hours after LC was documented in 4 articles.^[9-12] There was significant difference between the groups (WMD=-4.820, 95% CI: -9.037 to -0.603, $P=.025$; Fig. 7). A fixed-effects model was adopted because no statistical heterogeneity was detected between the articles ($\chi^2=0.13$, $df=3$, $I^2=0.0\%$, $P=.988$).

3.4.6. Postoperative opioid requirements at 24 hours. A total of 4 studies^[9-12] provided opioid requirements at 24 hours postoperatively. There was a statistically significant difference between the groups with respect to the opioid requirements at 24 hours (WMD=-3.227, 95% CI: -5.670 to -0.784, $P=.010$; Fig. 8). A fixed-effects model was used ($\chi^2=2.99$, $df=3$, $I^2=0.0\%$, $P=.394$).

3.5. Secondary outcomes

3.5.1. Length of hospital stay. Four articles^[9-12] reported length of hospital stay after LC. There was no heterogeneity among the articles and a fixed-effects model was adopted ($\chi^2=1.41$, $df=3$, $I^2=0.0\%$, $P=.702$). Meta-analysis revealed that there was no significant difference in length of hospital stay (WMD=0.069, 95% CI: -0.180 to 0.318, $P=.586$; Fig. 9).

3.5.2. Opioid-related adverse effects. Four studies^[9-12] reported the outcome of opioid-related adverse effects including nausea, vomiting and pruritus after LC. A fixed-effects model was adopted because no significant heterogeneity was found among the studies ($\chi^2=1.88$, $df=11$, $I^2=0.0\%$, $P=.999$). There was significant difference regarding the risk of opioid-related adverse effects (RD=-0.121, 95% CI: -0.181 to -0.061, $P=.000$; Fig. 10).

3.5.3. Incidence of venous thromboembolism. Four studies^[9-12] showed the postoperative complications including

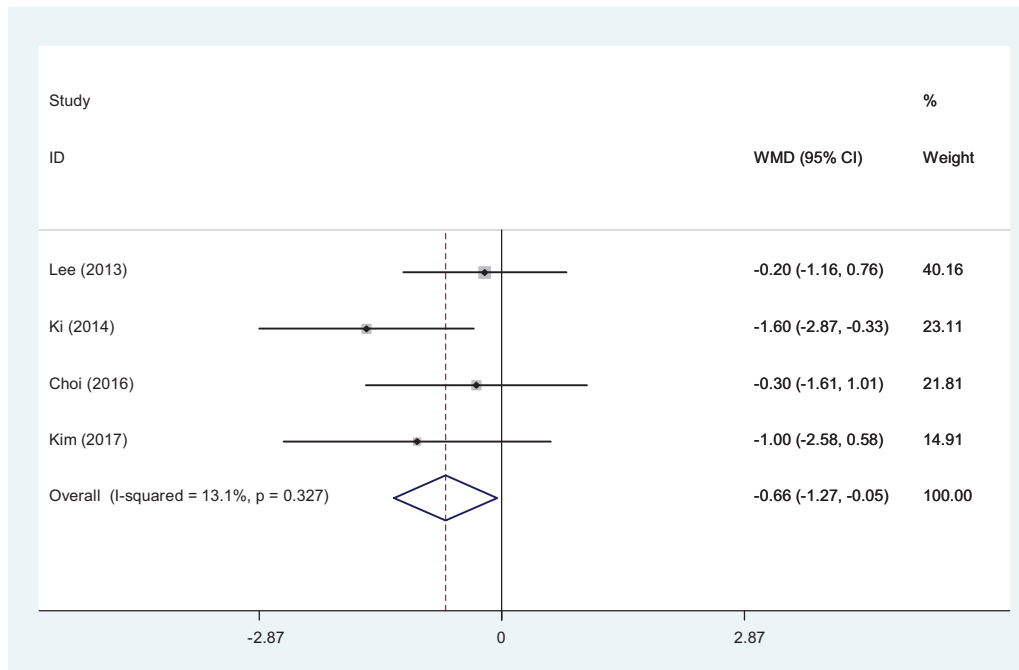


Figure 3. Forest plot diagram showing VAS scores at 6 hours after LC. VAS=visual analog scale, WMD=weigh weighted mean difference, .

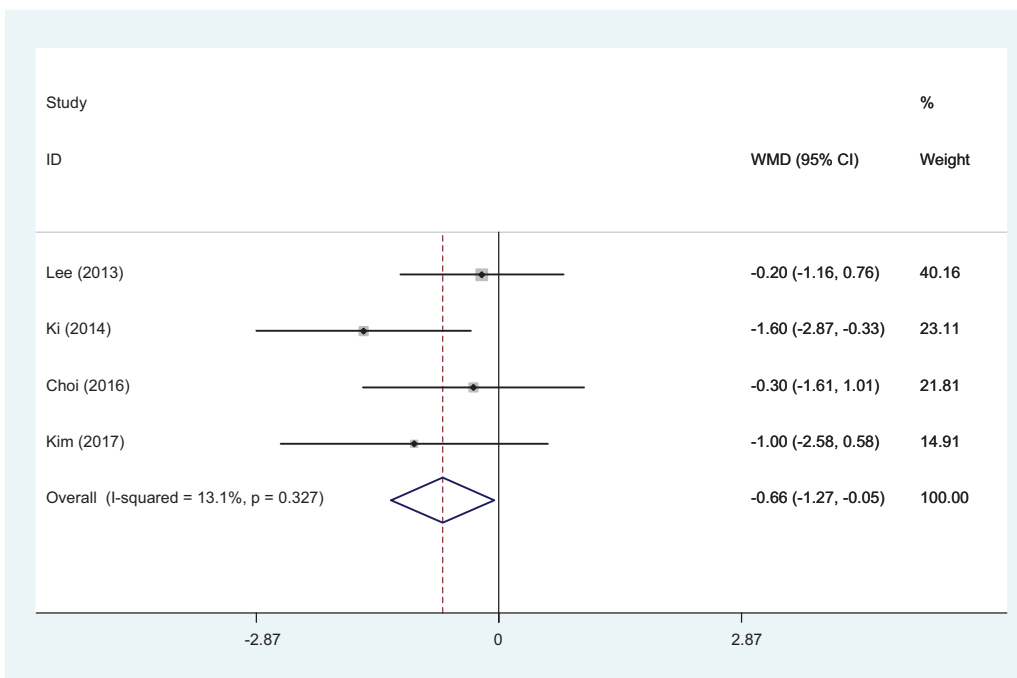


Figure 4. Forest plot diagram showing VAS scores at 12 hours after LC. VAS=visual analog scale, WMD=weigh weighted mean difference.

deep venous thrombosis (DVT) and pulmonary embolism (PE). A fixed-effect model was adopted ($\chi^2=1.13$, $df=7$, $I^2=0.0\%$, $P=.992$). There was no significant difference between groups regarding the incidence of venous thromboembolism (RD=-0.000, 95% CI: -0.032 to 0.032, $P=.996$; Fig. 11).

3.5.4. Evidence level and recommendation strengths. Quality of evidence for main outcomes in our study was evaluated by the GRADE system. The evidence quality for each outcome was moderate, which meant that further research was likely to significantly change confidence in the effect estimate, and may change the estimate (Table 2).

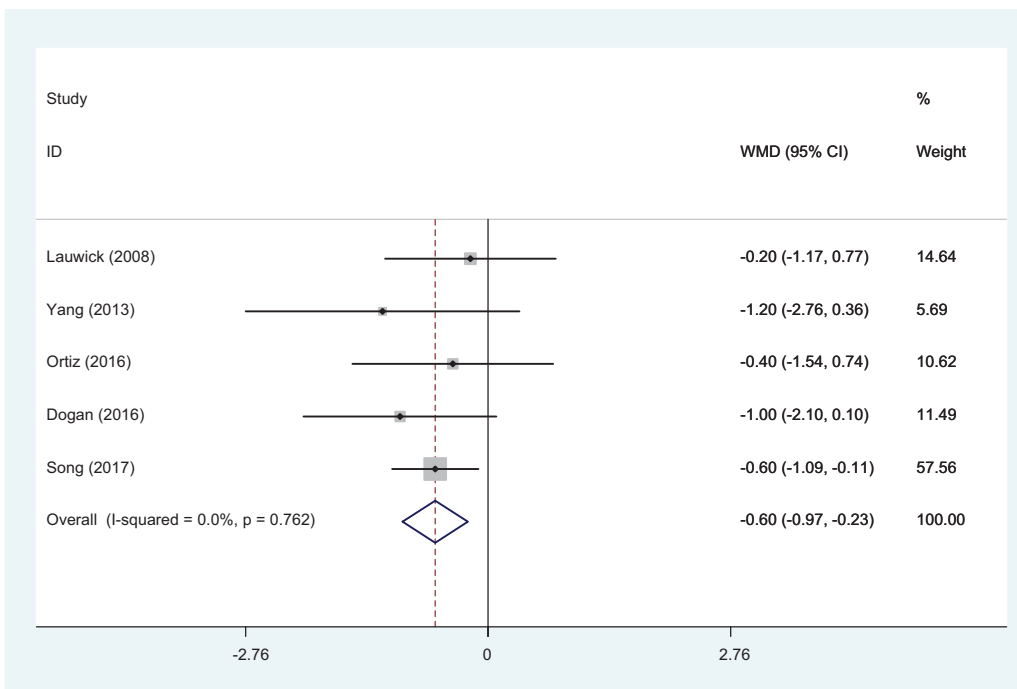


Figure 5. Forest plot diagram showing VAS scores at 24 hours after LC. VAS=visual analog scale, WMD=weigh weighted mean difference.

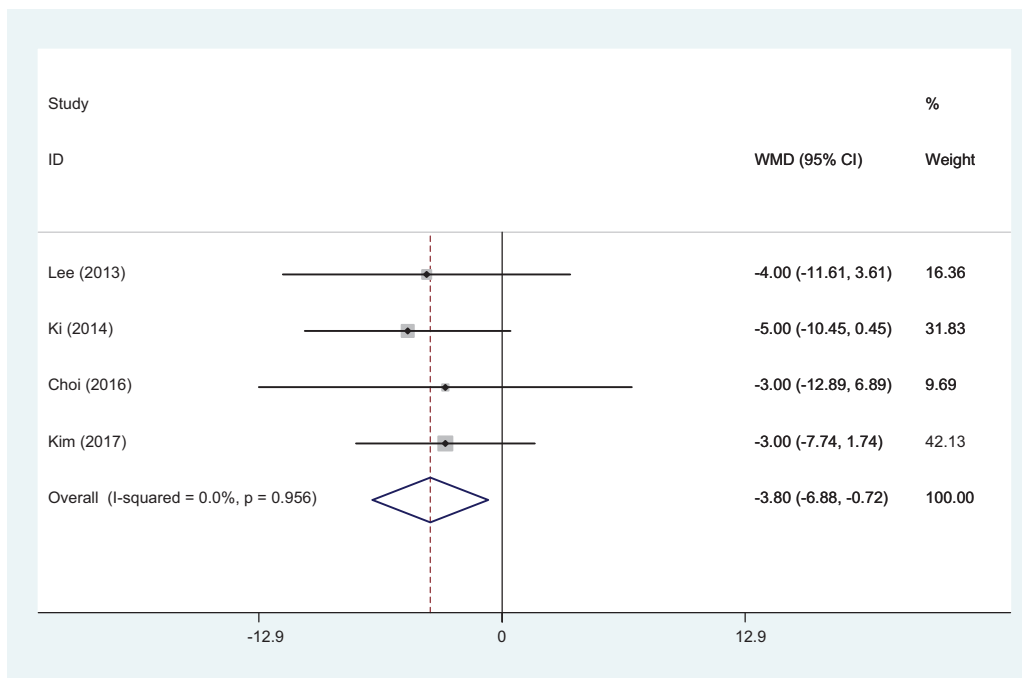


Figure 6. Forest plot diagram showing opioid requirement at 6 hours after LC. WMD=weigh weighted mean difference.

4. Discussion

To the best of our knowledge, this is the first meta-analysis of RCTs to evaluate the efficacy and safety of intravenous nefopam for reducing postoperative pain and opioid requirements after LC. The most important finding of the present meta-analysis is that intravenous nefopam is associated with a significant reduction in postoperative VAS scores and consumption require-

ments compared with controls. Additionally, there is a lower risk of opioid-related adverse effects. The overall evidence quality is moderate, which means that further research is likely to significantly change confidence in the effect estimate, and may change the estimate.

Pain control after LC has become a serious clinical problem. Although LC provides the possibility of minimal invasive and

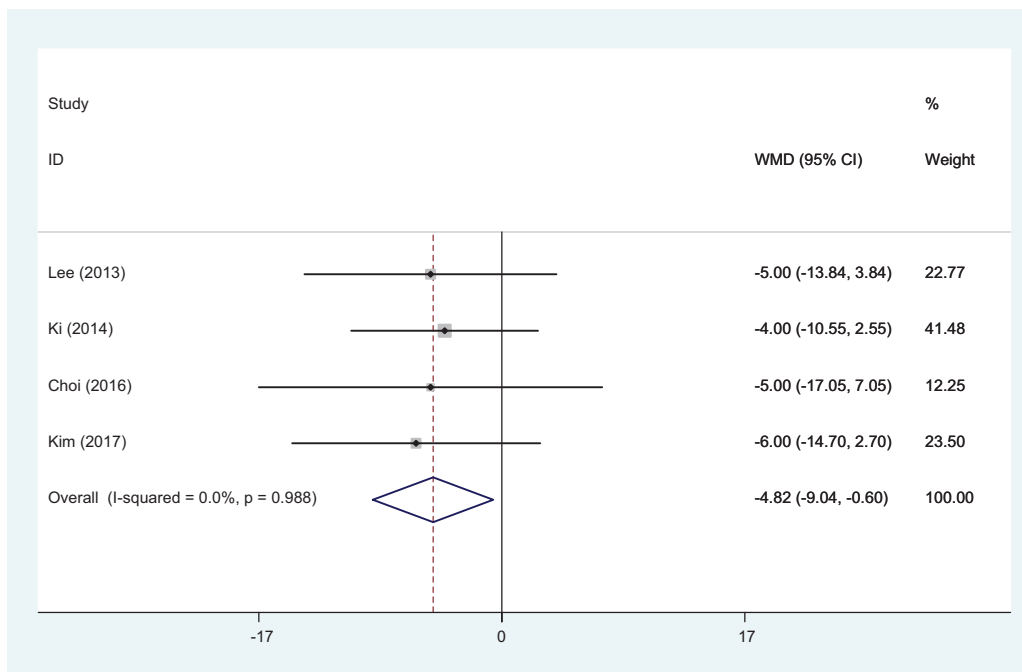


Figure 7. Forest plot diagram showing opioid requirement at 12 hours after LC. WMD=weigh weighted mean difference.

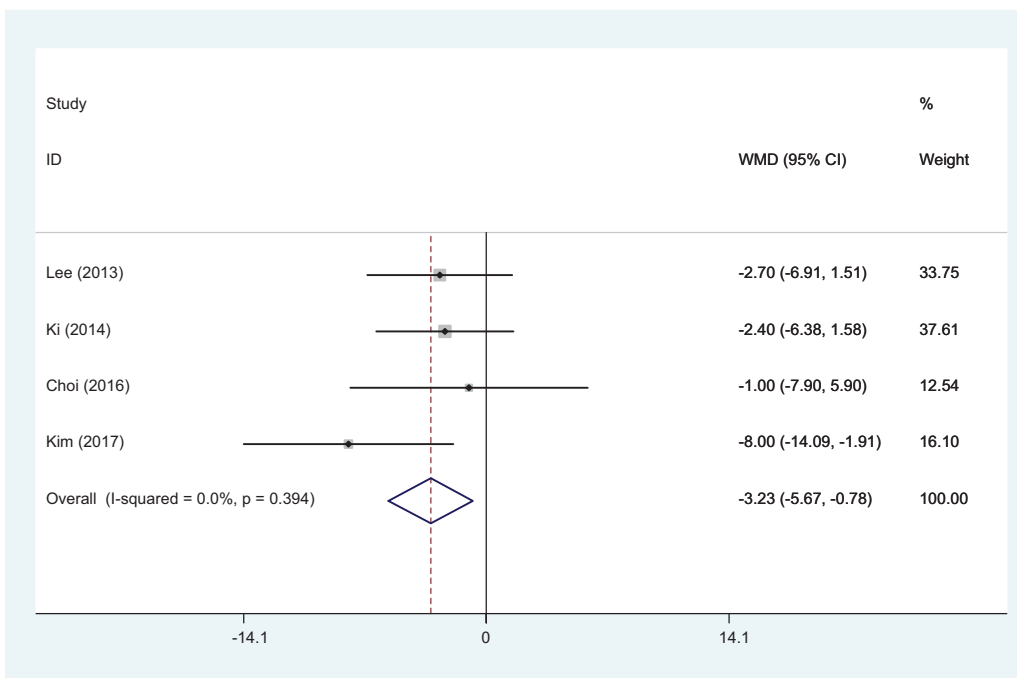


Figure 8. Forest plot diagram showing opioid requirement at 24 hours after LC. WMD=weigh weighted mean difference.

early discharge from hospital, moderate to severe postoperative pain still occurs in 50% to 70% of patients.^[13] It is well-documented that ideal pain management contributes to rapid recovery and less postoperative complications. However, single-mode analgesia is not enough to provide satisfactory outcomes, and a multimodal analgesic regime has become an established practice recommended to provide pain relief, inhibit adverse

reactions, reduce surgical stress response, and improve clinical outcomes. Nefopam was first introduced as an antidepressant, then it was reported to be efficacious in preventing postsurgical hyperalgesia. It is considered a potent nonopioid analgesic with supraspinal and spinal sites of action.^[14,15] In rats, nefopam is shown to modulate the N-methyl-D-aspartic acid receptors, inhibiting c-Fos expression in the dorsal horn of the spinal cord

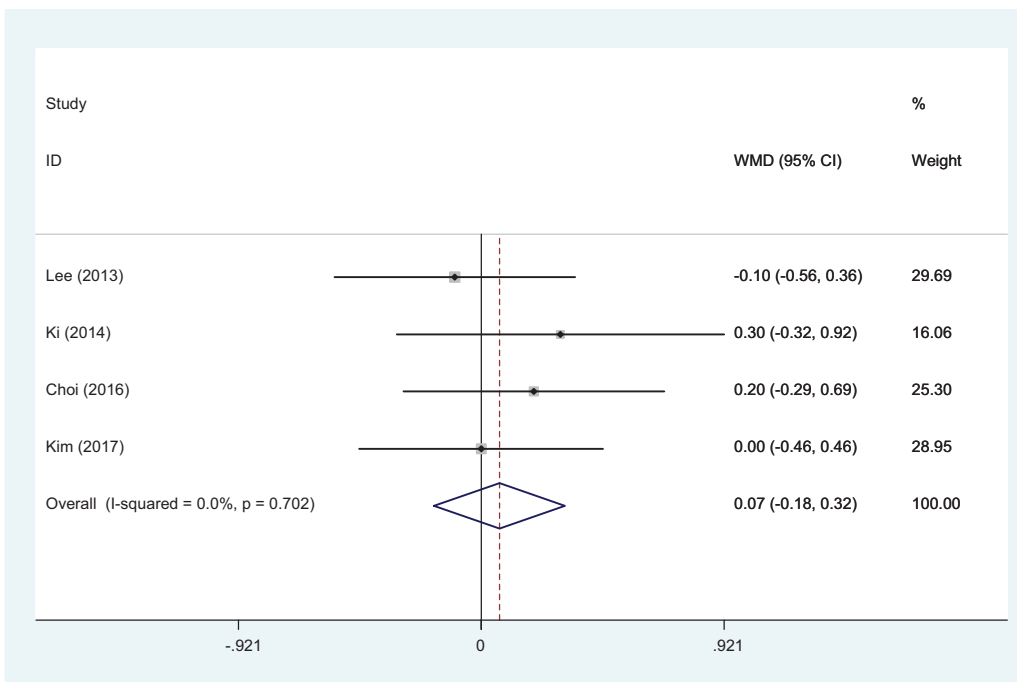


Figure 9. Forest plot diagram showing length of hospital stay. WMD=weigh weighted mean difference.

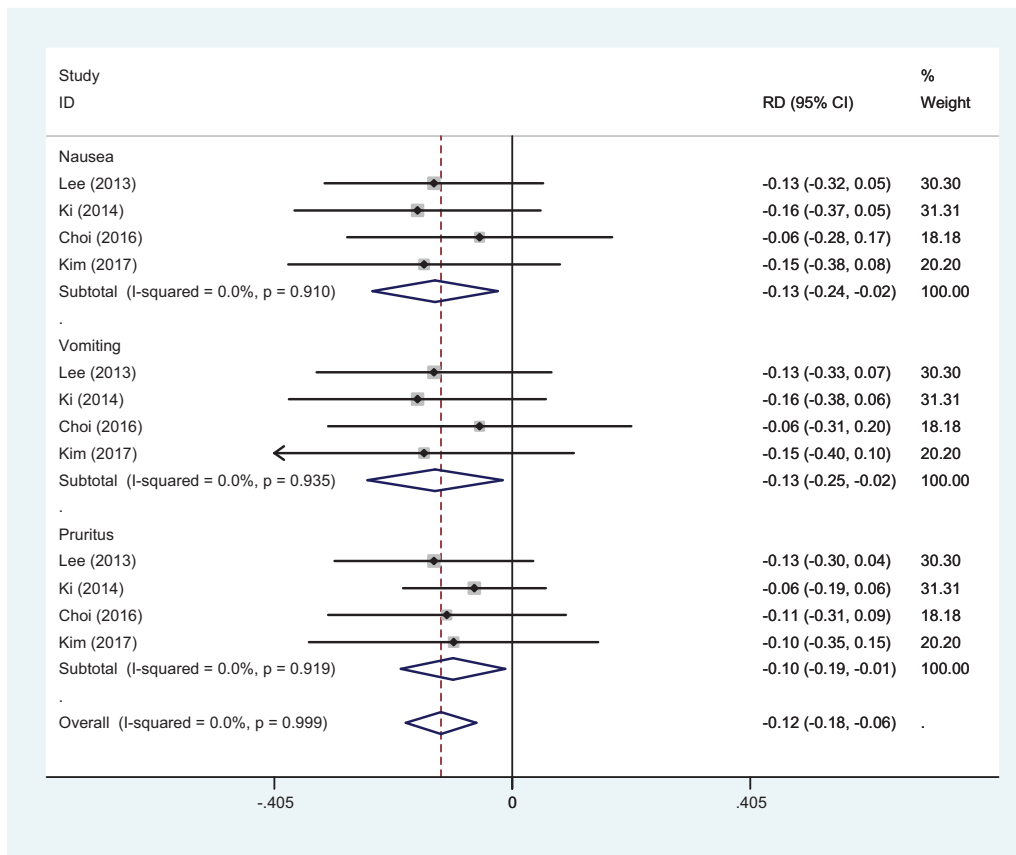


Figure 10. Forest plot diagram showing opioid-related adverse effects. RD = risk difference.

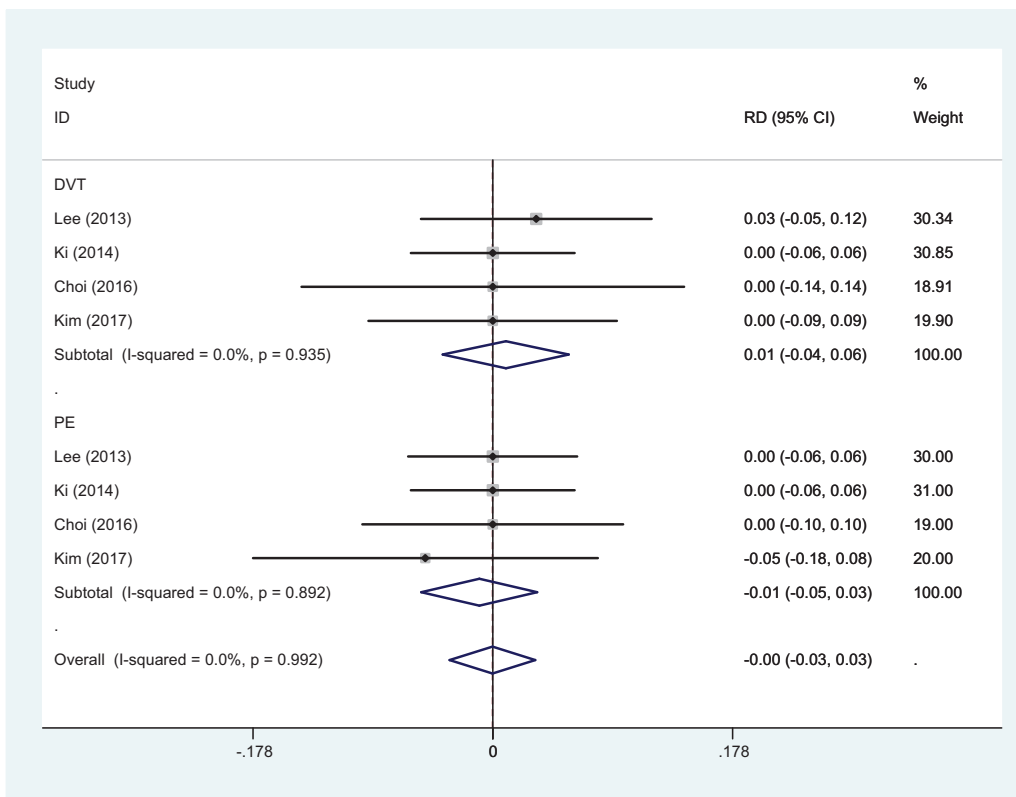


Figure 11. Forest plot diagram showing postoperative complications. DVT = deep venous thrombosis, PE = pulmonary embolism, RD = risk difference.

Table 2
The GRADE evidence quality for main outcome.

Quality assessment		No of patients				Effect	Quality	Importance			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision				Nefopam groups	Control groups	
VAS at 6 hours	4	RCT	Serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	99	99	WMD = -0.736, 95% CI: -1.296 to -0.176	Moderate	Critical
VAS at 12 hours	4	RCT	Serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	99	99	WMD = -0.665, 95% CI: -1.275 to -0.054	Moderate	Critical
VAS at 24 hours	4	RCT	Serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	99	99	WMD = -0.757, 95% CI: -1.334 to -0.179	Moderate	Critical
Opioid requirements at 6 hours	4	RCT	Serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	99	99	WMD = -3.800, 95% CI: -6.877 to -0.723	Moderate	Critical
Opioid requirements at 12 hours	4	RCT	Serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	99	99	WMD = -4.820, 95% CI: -9.037 to -0.603	Moderate	Critical
Opioid requirements at 24 hours	4	RCT	Serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	99	99	WMD = -3.227, 95% CI: -5.670 to -0.784	Moderate	Critical

RCT = randomized controlled trial, RD = risk difference, VAS = visual analog scale, WMD = weigh weighted mean difference.

and relieving allodynia.^[16] Although it is widely used in postoperative acute pain management after surgery, debate still remains. Kim et al^[12] reported that intraoperative nefopam infusion following LC could decrease pain during the early postoperative period. However, Cuvillon et al^[17] suggested that nefopam in combination with paracetamol has no benefit after abdominal surgery. Because of the controversy, we performed the present meta-analysis from published RCTs, and it indicates that intravenous nefopam is associated with a reduction in VAS scores at 6, 12, and 24 hours with clinical significance after LC. Several factors may affect the results of our study, such as the dose of nefopam and preoperative medication. However, only 4 studies are included and it is insufficient to perform a subgroup analysis. More RCTs are required to explore the optimal dose of nefopam.

Opioids are commonly used for concomitant pain management after laparoscopic surgery.^[18] In addition, the analgesic effect of the additional opioids provides a long postoperative period without any pain experienced by the patients. However, published articles have reported that opioids are associated with many adverse reactions including gastrointestinal events, headache, pruritus, consumption, and respiratory depression.^[19-21] Drug dependence is also a major concern for the surgeon and anesthetist. Reducing narcotic consumption contributes to early mobilization and recovery. Nefopam is reported to have a morphine-sparing effect of 30% to 50%.^[22,23] Previous articles comparing nefopam and opioids showed 20mg of nefopam was approximately equivalent to 12mg of morphine in postoperative analgesia.^[24] Currently, the use of nefopam for reducing opioid requirements after LC remains controversial, owing to the limited number of published studies. Meta-analysis can enhance statistical power and enlarger sample size, which may provide more reliable evidence. A total of 4 RCTs with 198 patients report opioid consumption after LC. The present meta-analysis indicates that intravenous nefopam infusion could significantly decrease opioid requirements. Further investigation is still required because only 4 RCTs are included.

Analgesic effect is not the only concern when evaluating nefopam. Gastrointestinal discomfort is a common adverse effect related to opioids. Reducing opioid requirements can subsequently decrease such adverse effects. The present meta-analysis indicates that the use of nefopam could significantly reduce the incidence of nausea, vomiting, and pruritus. Additionally, no increased risk of venous thromboembolism was found between groups. However, a large sample size of RCTs with long term follow-up is required.

Several limitations in our study should be noted: only 4 RCTs were included, and the sample sizes in these trials was small; heterogeneity caused by some factors, such as the dose of nefopam and comparable baseline, which may have affected the results; subgroup analysis was not performed regarding the main outcomes; short term follow-up resulted in an underestimation of complications; and all included RCTs were English publications, thus, publication bias was unavoidable.

5. Conclusion

Intravenous nefopam infusion resulted in significant reduction in postoperative pain scores and opioid requirements while decreasing opioid-related adverse effects. Additionally, no increased risk of venous thromboembolism was found. The current evidence suggests that more RCTs will be needed in further investigations.

5.1. Authors' contributions

SHS designed the study. ZS and TCZ analyzed the data and finished the manuscript. ZS and TCZ revised the manuscript. All authors read and approved the final manuscript.

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