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Intravenous lidocaine infusion for pain control after laparoscopic cholecystectomy

A meta-analysis of randomized controlled trials

Ji-Bo Zhao, MM[a], Yuan-Li Li, MM[b], Ye-Ming Wang, MM[a], Jin-Liang Teng, MM[a], Deng-Yun Xia, MM[a], Jin-Shi Zhao, MB[a], Fu-Long Li, MM[a,*]

Abstract

Background: This meta-analysis aimed to assess the efficiency and safety of intravenous infusion of lidocaine for pain management after laparoscopic cholecystectomy (LC).

Methods: A systematic search was performed in PubMed (August 1966–2017), Medline (August 1966–2017), Embase (August 1980–2017), ScienceDirect (August 1985–2017), and the Cochrane Library. Only randomized controlled trials (RCTs) were included. Fixed/random effect model was used according to the heterogeneity tested by I2 statistic. Meta-analysis was performed using Stata.11.0 software.

Results: A total of 5 RCTs were retrieved involving 274 patients. The present meta-analysis indicated that there were significant differences between groups in terms of visual analog scale scores at 12hours (weighted mean difference [WMD]=−0.743, 95% CI: −1.246 to −0.240, $P=.004$), 24hours (WMD=−0.712, 95% CI: −1.239 to −0.184, $P=.008$), and 48hours (WMD=−0.600, 95% CI: −0.972 to −0.229, $P=.002$) after LC. Significant differences were found regarding opioid consumption at 12hours (WMD=−3.136, 95% CI: −5.591 to −0.680, $P=.012$), 24hours (WMD=−4.739, 95% CI: −8.291 to −1.188, $P=.009$), and 48hours (WMD=−3.408, 95% CI: −5.489 to −1.326, $P=.001$) after LC.

Conclusion: Intravenous lidocaine infusion significantly reduced postoperative pain scores and opioid consumption after LC. In addition, there were fewer adverse effects in the lidocaine groups. Higher quality RCTs are still required for further research.

Abbreviations: LC = laparoscopic cholecystectomy, LOS= length of stay, RCT= randomized controlled trials, VAS = visual analogy score.

Keywords: laparoscopic cholecystectomy, lidocaine, meta-analysis, pain control

1. Introduction

Laparoscopic cholecystectomy (LC) was first performed in 1987[1] and now it has become a successful surgical procedure for the treatment of cholelithiasis, cholecystitis, and biliary colic.[2] It has shown improved outcomes compared to conventional open procedures and replaced open cholecystectomy as the first choice. It was reported that >600,000 LCs were performed in the United States annually which predicting an increasing trend and requirement for the next few years.[3] However, LC was reported to be associated with postoperative pain from moderate-to-intense degrees which delayed postoperative recovery and discharge from the day-surgery unit, leading to unanticipated hospital admission.[4]

Pain management after major abdominal surgery has become a serious clinical problem. Many strategies have been implemented to reduce postoperative pain following LC, including steroidal anti-inflammatory drugs, administration of opioid, and local anesthesia.[5–7] However, none of them has shown consistent efficacy. Thus, multimodal analgesia regime was recommended for pain management after laparoscopic surgery.[8,9] Recently, intravenous lidocaine infusion in the intraoperative has shown improved outcome in reducing postoperative pain. Koppert et al[10] reported that the perioperative administration of systemic small-dose lidocaine reduces pain and morphine use during surgery. Vigneault et al[11] demonstrated that perioperative intravenous lidocaine reduced postoperative pain and opioid requirement, as well as hospital length of stay (LOS). The possible mechanism appears to be due to a reduction of neural responses to pain by inhibiting nerve conduction. Besides, lidocaine has powerful anti-inflammatory properties.

Currently, the intravenous infusion of lidocaine in the setting of postoperative relief of pain after LC was seldom reported and the beneficial effect remained controversial. There was a lack of reliable scientific evidence. Therefore, we performed a meta-analysis from randomized controlled trials (RCTs) to assess the efficiency and safety of intravenous infusion of lidocaine for pain management after LC.

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J-BZ and Y-LL contributed equally to this work.

The authors have no conflict of interest to disclose.

[a] Department of Anesthesiology, [b] Department of Critical Care Medicine, The First Affiliated Hospital of Hebei North University, Zhangjiakou, Hebei, China.

[*] Correspondence: Fu-Long Li, Department of Anesthesiology, The First Affiliated Hospital of Hebei North University, Zhangjiakou, Hebei, China (e-mail: a844092266@126.com).

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2. Methods

This study was reported according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Ethical approval was not required because this was a meta-analysis of published articles.

2.1. Search strategy

We conducted electronic searches of PubMed (August 1966–2017), Medline (August 1966–2017), Embase (August 1980–2017), ScienceDirect (August 1985–2017), and the Cochrane Library. The following keywords were used in combination with Boolean operators AND or OR: "laparoscopic cholecystectomy", "lidocaine," and "pain control." References of the included articles were also scanned for potentially relevant studies. No restrictions were placed on the publication language.

2.2. Inclusion criteria and study selection

(1) Participants: Published literatures enrolling adult patients who prepared for LC; (2) Interventions: The intervention group received intravenous infusion of lidocaine in the setting of postoperative relief of pain; (3) Comparisons: The control group received normal saline; (4) Outcomes: Pain scores, opioid consumption, length of stay, and postoperative complications such as opioid-related adverse effects; (5) Study design: RCTs were regarded as eligible in the study. Articles would be excluded from the present meta-analysis for case reports, conference abstract, or review articles. Two reviewers independently scanned the abstracts of the potential articles identified by the above searches. Subsequently, the full text of the studies that met the inclusion criteria was screened and a final decision was made. A senior author had the final decision in any case of disagreement regarding which studies to include.

2.3. Date extraction

The included studies were examined by 2 investigators and key data were extracted including first author name, samples size, published year, baseline characteristics, and intervention of each group. The primary outcomes were visual analogy score (VAS) scores and opioid consumption. The secondary outcomes were LOS and opioid-related adverse effects.

2.4. Assessment of methodological quality

A quality assessment of each RCT was performed by 2 reviewers based on the Cochrane Handbook for Systematic Reviews of Interventions. Disagreement was resolved by consulting a senior reviewer. We created a "risk of bias" table that included the following elements: random sequence generation, allocation concealment, blinding, incomplete outcome data, free of selective reporting, and other bias.

The quality of the evidence for the main outcomes in present meta-analysis was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system including the following items: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The recommendation level of evidence is classified into the following categories: (1) high, which means that further research is unlikely to change confidence in the effect estimate; (2) moderate, which means that further research is likely to significantly change confidence in the effect estimate but may change the estimate; (3) low, which means that further research is likely to significantly change confidence in the effect estimate and to change the estimate; and (4) very low, which means that any effect estimate is uncertain.

2.5. Data analysis and statistical methods

The data were pooled using Stata V.12.0 (The Cochrane Collaboration, Oxford, UK). After extracting the data from the included studies, we exported the means, SDs, and sample sizes of groups into Stata V.12.0 to determine the heterogeneity. Statistical heterogeneity was assessed based on the P and I^2 values using the standard χ^2 test. When $I^2 \geq 50\%$ or $P < .1$, significant heterogeneity was indicated and a random-effects model was applied for the meta-analysis. Otherwise, a fixed-effects model was used. Dichotomous outcomes (i.e., complications) were expressed as risk differences (RDs) with 95% confidence intervals (CIs). For continuous outcomes (i.e., pain scores), weighted mean differences (WMDs) and 95% confidence intervals (CIs) were calculated.

3. Results

3.1. Search result

A total of 350 studies were identified through the initial search. By scanning the abstracts, 345 reports that did not met inclusion criteria were excluded from the current meta-analysis. No gray studies were included. Finally, 5 RCTs[12–16] published between 2008 and 2017 were included in the present meta-analysis which contained 138 patients in combined groups and 136 patients in controls. The literature research and selection process are presented in a PRISMA flow diagram (Fig. 1)

3.2. Study characteristics

Only patients prepared to undergo LC were included in our study. The sample sizes ranged from 43 to 71 patients and average age ranged from 44 to 54. In these articles, the experimental groups received the intravenous infusion of lidocaine for pain management and the control groups received normal saline. The characteristics of the included studies were reported in Table 1. Statistically similar baseline characteristics were observed between groups.

3.3. Risk of bias

The Cochrane Handbook for Systematic Review of Interventions was consulted to assess risk of bias of the RCTs. All RCTs involved the correct methods to generate the random sequence and 4 studies[13–16] described that allocation concealment was achieved by closed envelope. Four articles[12,14–16] reported blinding for participants and study personnel, and 4 studies[13–16] applied blinding for the assessors. Low risk of bias due to incomplete outcome data or selective outcome reporting was detected. The methodological quality of the included studies is presented in Table 2. Judgments regarding each risk of bias item are presented as percentages across all the included studies in Table 3.

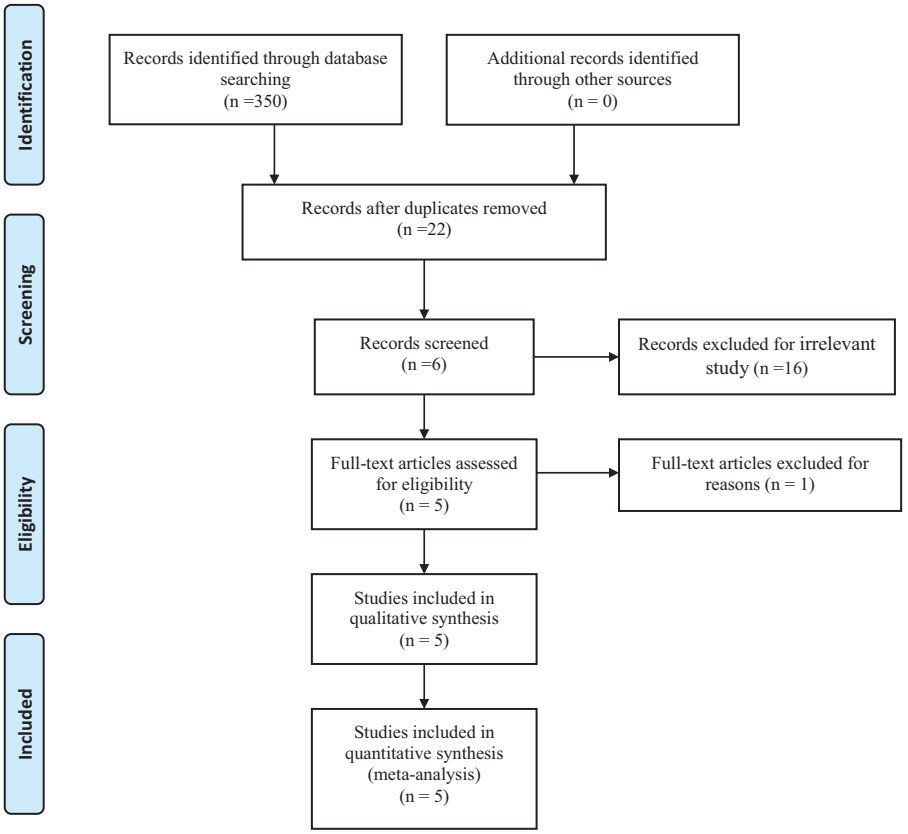


Figure 1. Flow diagram.

3.4. Outcomes for meta-analysis

3.4.1. VAS scores at 12 hours. Five studies with 274 patients showed the VAS scores at 12 hours after LC. A fixed-effects model was used because no significant heterogeneity was found among the studies ($\chi^2 = 1.40$, df = 4, $I^2 = 0\%$, $P = .844$). The pooled results demonstrated that VAS scores at 12 hours were significantly higher in the control groups than in the lidocaine groups (WMD = −0.743, 95% CI: −1.246 to −0.240, $P = .004$; Fig. 2).

3.4.2. VAS scores at 24 hours. Five studies with 274 patients reported the outcome of VAS scores at 24 hours after LC. No

Table 1

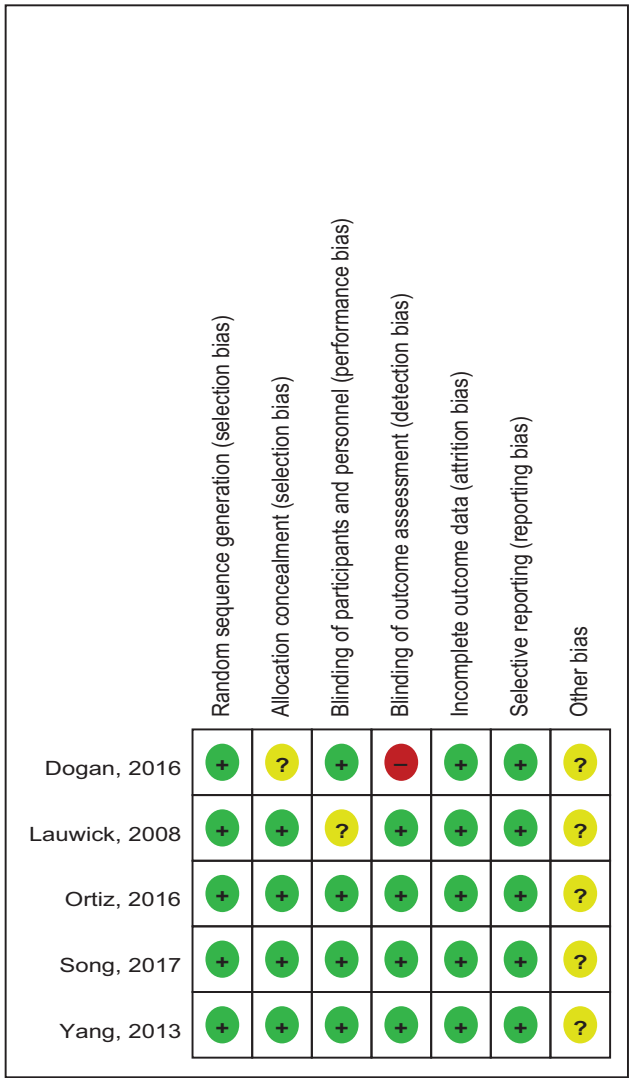
Trials characteristics.

Studies	Reference type	Location	Cases (E/C)	Mean age, years (E/C)	Female patient (E/C)	Experimental group	Control group	Concomitant pain control	Follow-up
Lauwick et al[13]	RCT	Canada	25/25	50/54	5/12	A bolus of lidocaine 1.5 mg/kg followed by a continuous infusion of lidocaine 2 mg/kg/hr	Normal saline	IV opioid	2 months
Yang et al[16]	RCT	Korea	26/24	49/48	16/12	An IV bolus injection of lidocaine (1.5 mg/kg) followed by a continuous IV lidocaine infusion at 2 mg/kg/h	Placebo	Patient-controlled analgesia	2 months
Ortiz et al[14]	RCT	Brazil	21/22	44/46	17/13	Lidocaine was administered in bolus of 1.5 mg/kg at the start of the procedure and maintained at a dose of 3 mg/kg/h	Saline solution	Patient-controlled analgesia	6 months
Dogan[12]	RCT	Turkey	30/30	45/47	16/14	An IV lidocaine infusion at a rate of 1.5 mg/kg/min for a total dose of 2 mg/kg/h	Normal saline	Patient-controlled analgesia	3 months
Song[15]	RCT	China	36/35	51/54	18/16	An IV bolus injection of lidocaine 1.5 mg/kg followed by a continuous IV infusion at the rate of 2 mg/kg/h via infusion pump	Normal saline	Patient-controlled analgesia	2 months

C = control group, E = experimental group, IV = intravenous, RCT= randomized controlled trial.

Table 2

Methodological quality of the randomized controlled trials.



significant heterogeneity was detected between groups ($\chi^2=7.59$, df=4, $I^2=47.3\%$, $P=.108$). There was significant difference in VAS scores at 24 hours between groups (WMD=−0.712, 95% CI: −1.239 to −0.184, $P=.008$; Fig. 3).

3.4.3. VAS scores at 48 hours. Five articles with 274 patients reported the outcome of VAS scores at 48 hours after LC. A fixed-effects model was used because no significant heterogeneity was found among the studies ($\chi^2=1.85$, df=4, $I^2=0\%$, $P=.762$). There was significant difference in VAS scores at 48 hours between groups (WMD=−0.600, 95% CI: −0.972 to −0.229, $P=.002$; Fig. 4).

3.4.4. Opioid consumption at 12 hours. Opioid consumption at 12 hours was reported in 5 articles. No significant heterogeneity was found among these studies ($\chi^2=0.63$, df=4, $I^2=0\%$, $P=.960$) and a fixed-effects model was used. A significant difference was detected between the 2 groups (WMD=−3.136, 95% CI: −5.591 to −0.680, $P=.012$; Fig. 5).

3.4.5. Opioid consumption at 24 hours. Five studies with 274 patients showed the outcome of opioid consumption at 24 hours after LC. In a fixed-effects model no significant heterogeneity was found ($\chi^2=0.21$, df=4, $I^2=0\%$, $P=.995$). There was a significant difference in opioid consumption at 24 hours between groups (WMD=−4.739, 95% CI: −8.291 to −1.188, $P=.009$; Fig. 6).

3.4.6. Opioid consumption at 48 hours. Five articles provided the data of opioid consumption at 48 hours after LC. A fixed-effects model was used because no significant heterogeneity was found ($\chi^2=1.98$, df=4, $I^2=0\%$, $P=.739$). There was a significant difference in opioid consumption at 48 hours between groups (WMD=−3.408, 95% CI: −5.489 to −1.326, $P=.001$; Fig. 7).

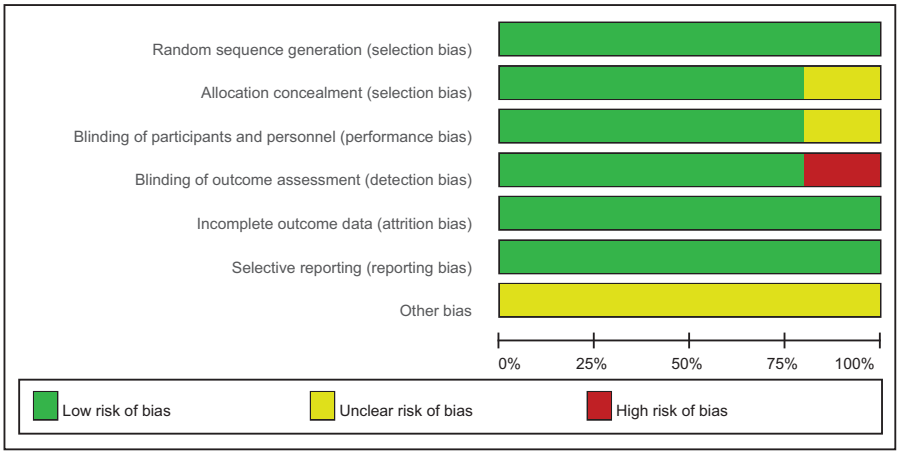
3.4.7. Length of hospital stay. Five studies reported the lengths of the hospital stay for the groups. No significant difference in the LOS was observed between the 2 groups (WMD=0.052, 95% CI: −0.061 to 0.165, $P=.364$; Fig. 8).

3.4.8. Nausea and vomiting. Five articles showed the postoperative complications of nausea and vomiting. A fixed-effects model was used ($\chi^2=0.24$, df=4, $I^2=0\%$, $P=.994$). Significant difference in the incidence of nausea and vomiting was found between the 2 groups (RD=−0.172, 95% CI: −0.275 to −0.070, $P=.001$; Fig. 9).

3.4.9. Ileus. Five articles showed the postoperative complications of ileus. A fixed-effects model was used ($\chi^2=0.07$, df=4, $I^2=0\%$, $P=.999$). A significant difference in the incidence of

Table 3

Risk of bias.



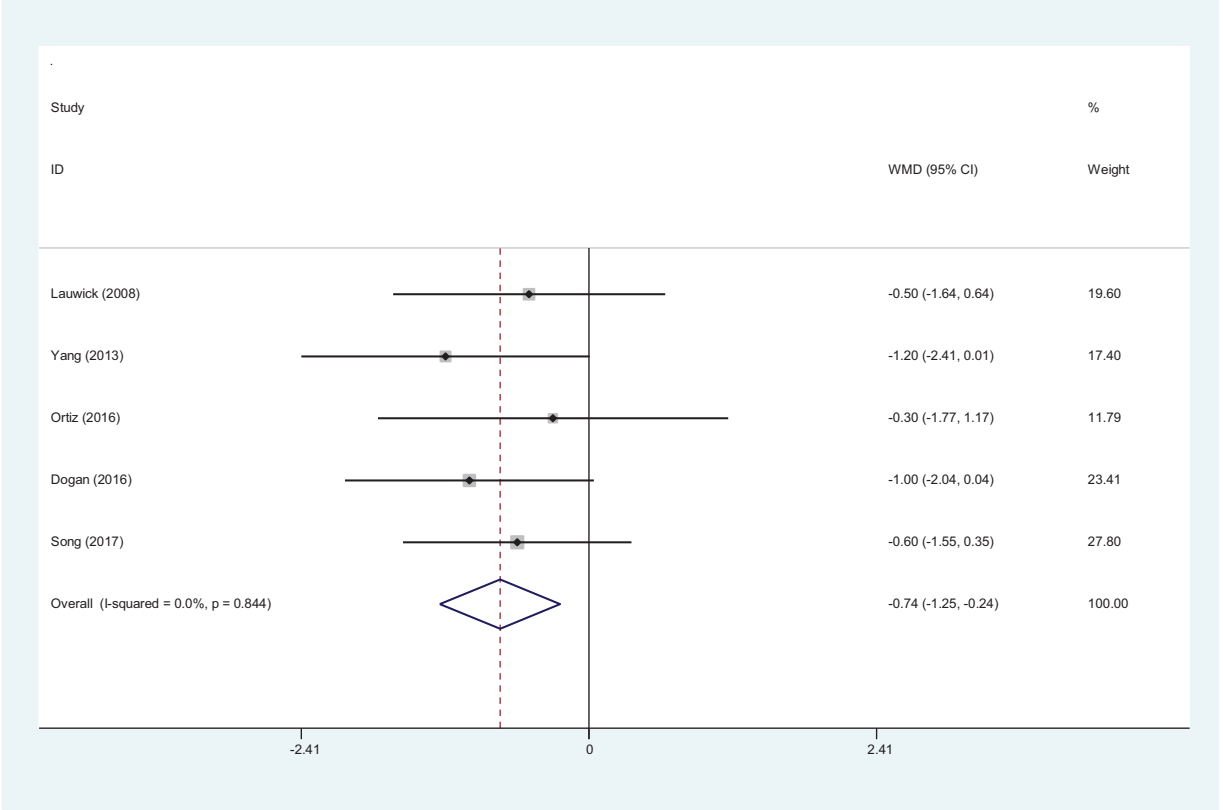


Figure 2. Forest plot diagram showing pain scores at 12 hours after LC. LC = laparoscopic cholecystectomy.

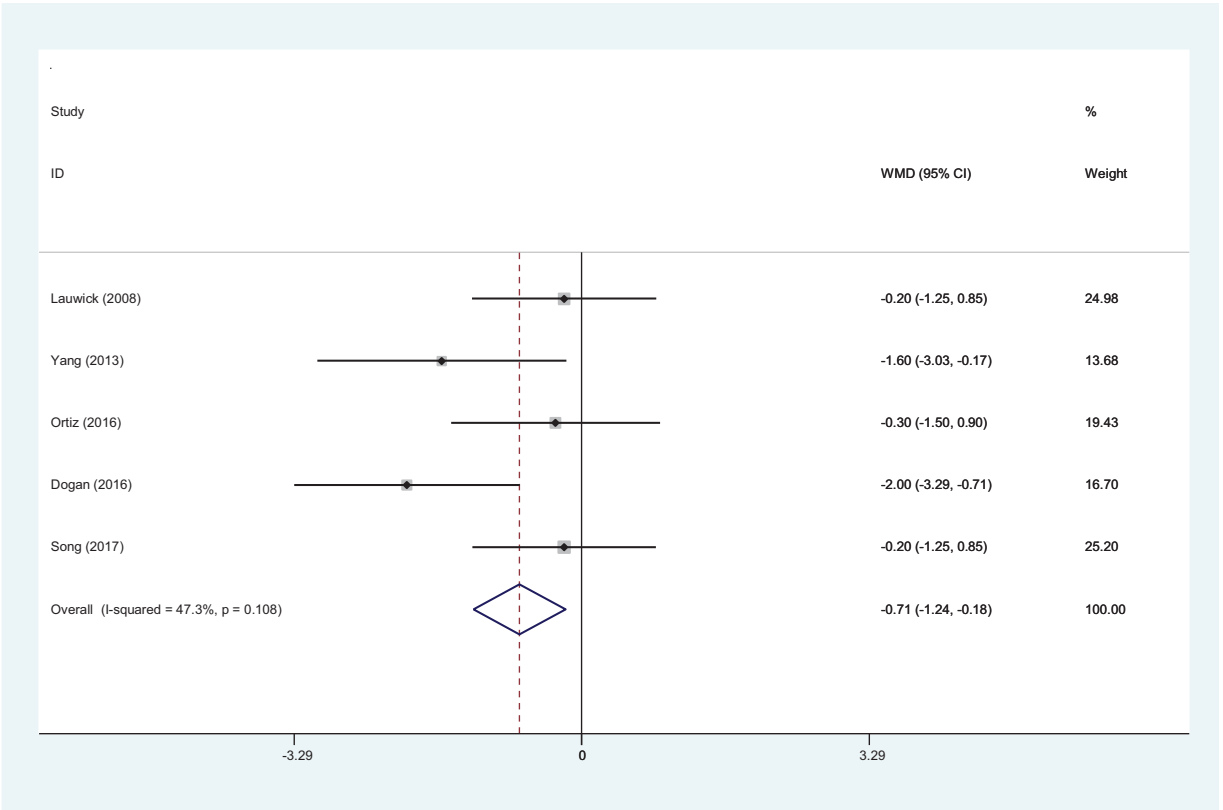


Figure 3. Forest plot diagram showing pain scores at 24 hours after LC. LC = laparoscopic cholecystectomy.

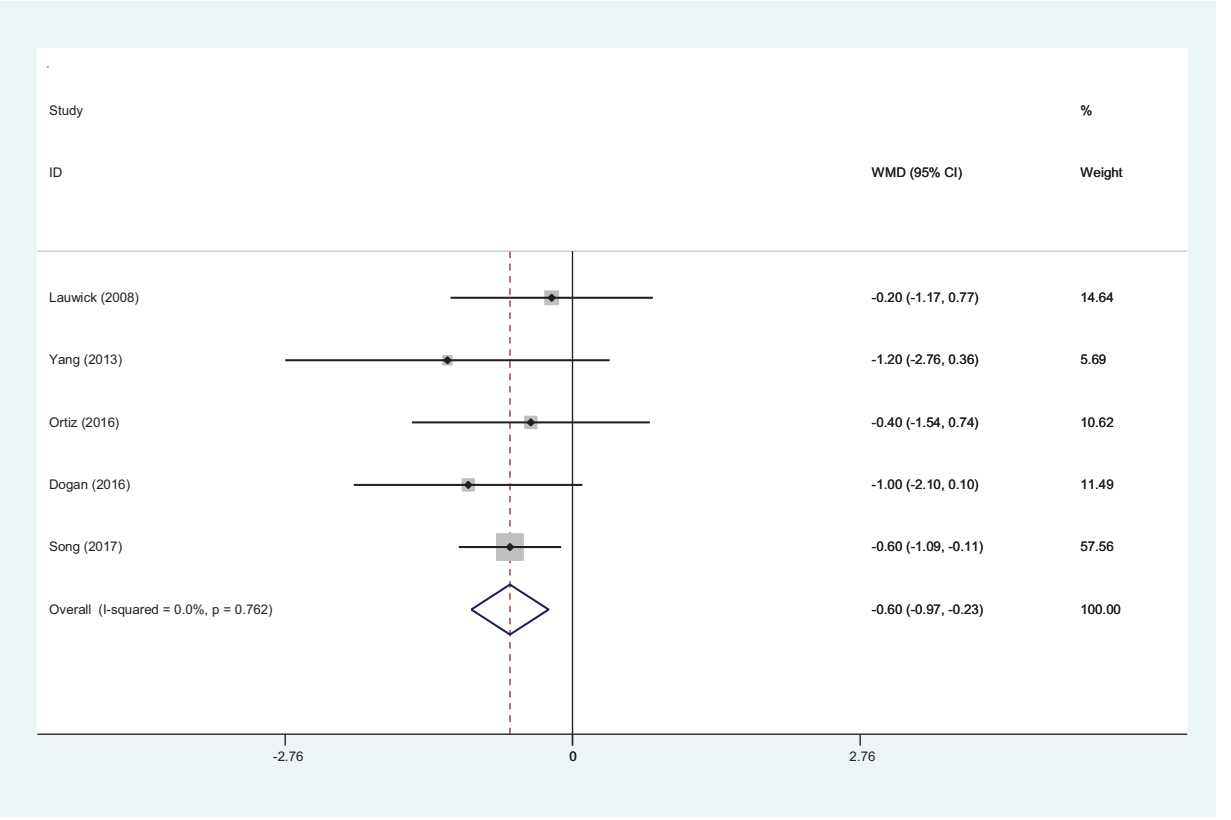


Figure 4. Forest plot diagram showing pain scores at 48 hours after LC. LC = laparoscopic cholecystectomy.

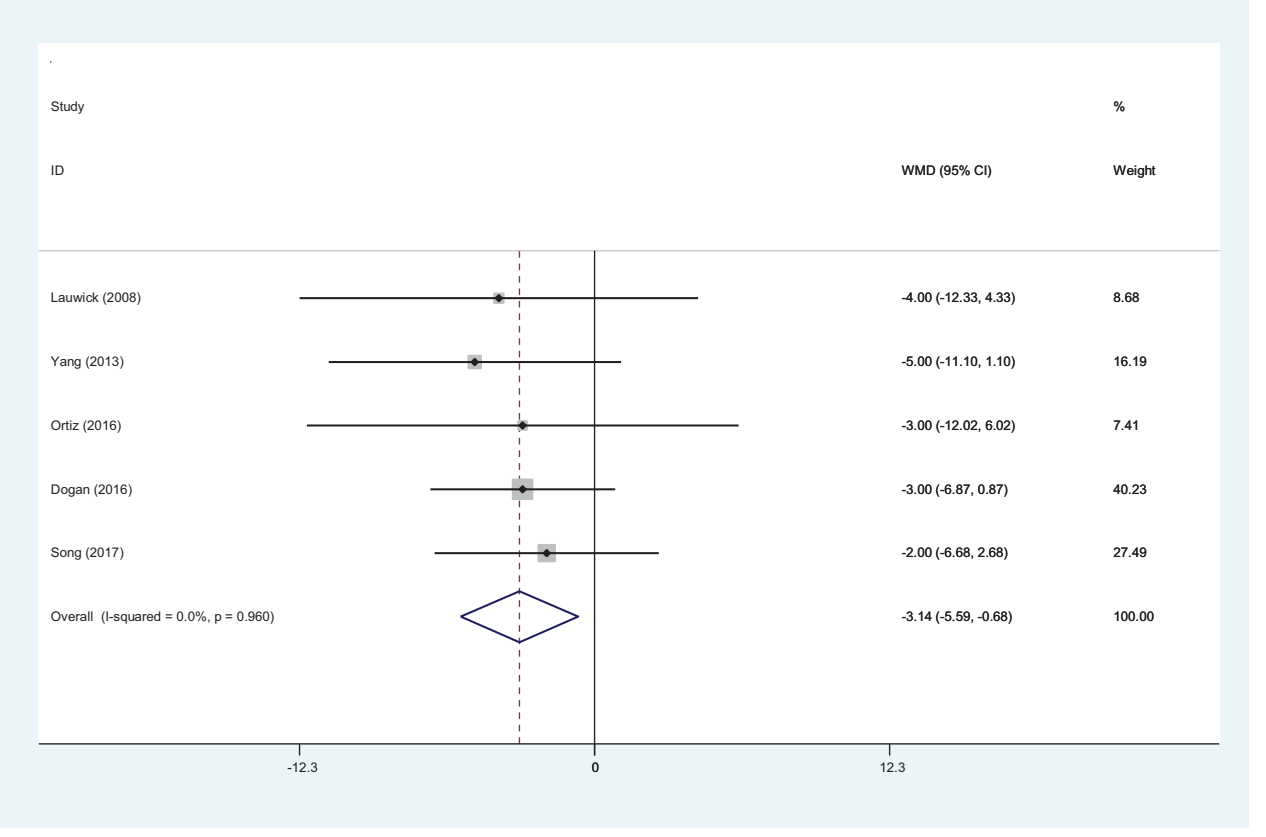


Figure 5. Forest plot diagram showing opioid consumption at 12 hours after LC. LC = laparoscopic cholecystectomy.

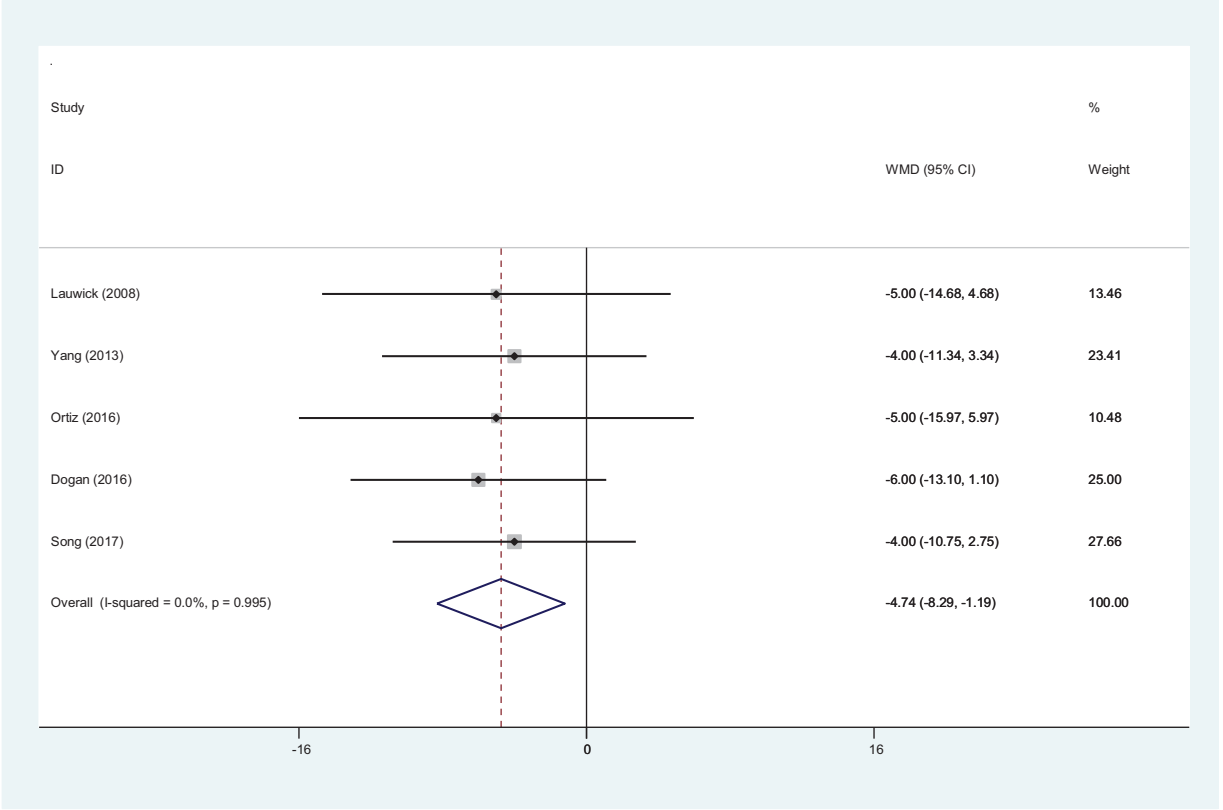


Figure 6. Forest plot diagram showing opioid consumption at 24 hours after LC. LC = laparoscopic cholecystectomy.

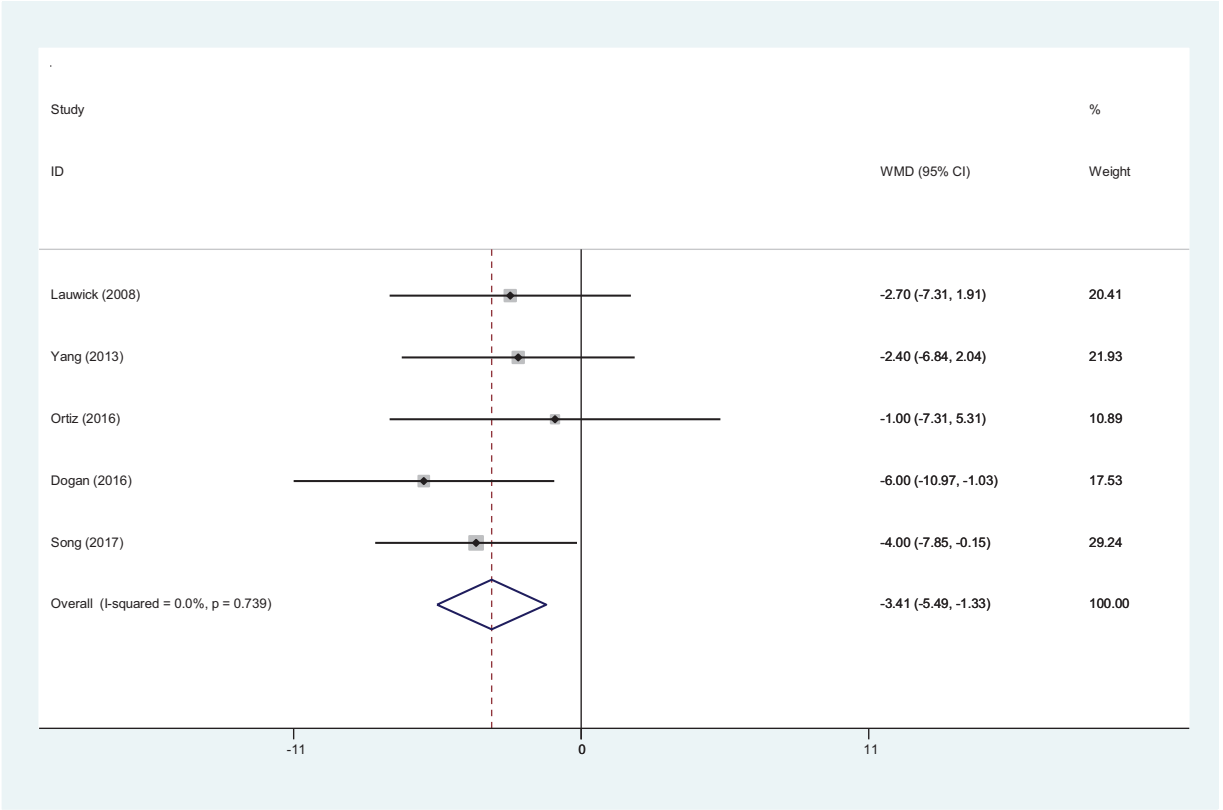


Figure 7. Forest plot diagram showing opioid consumption at 48 hours after LC. LC = laparoscopic cholecystectomy.

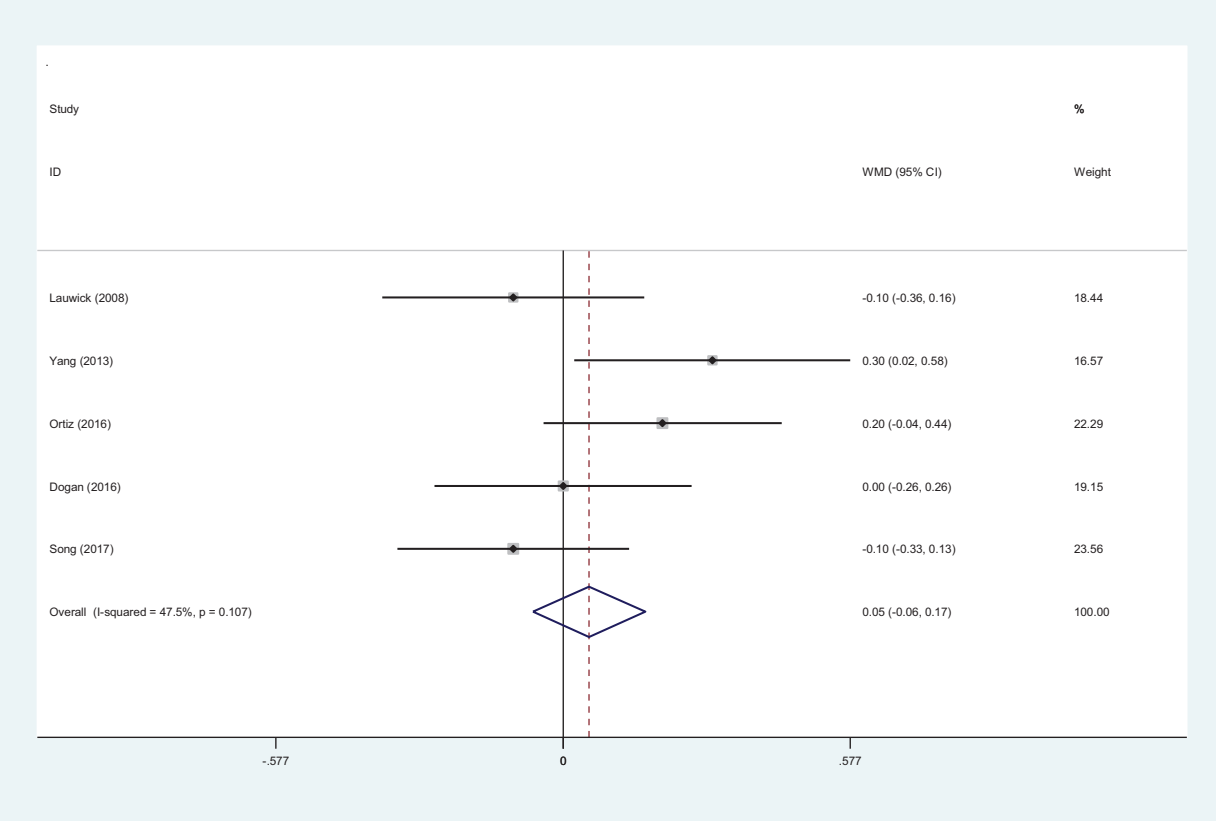


Figure 8. Forest plot diagram showing length of stay.

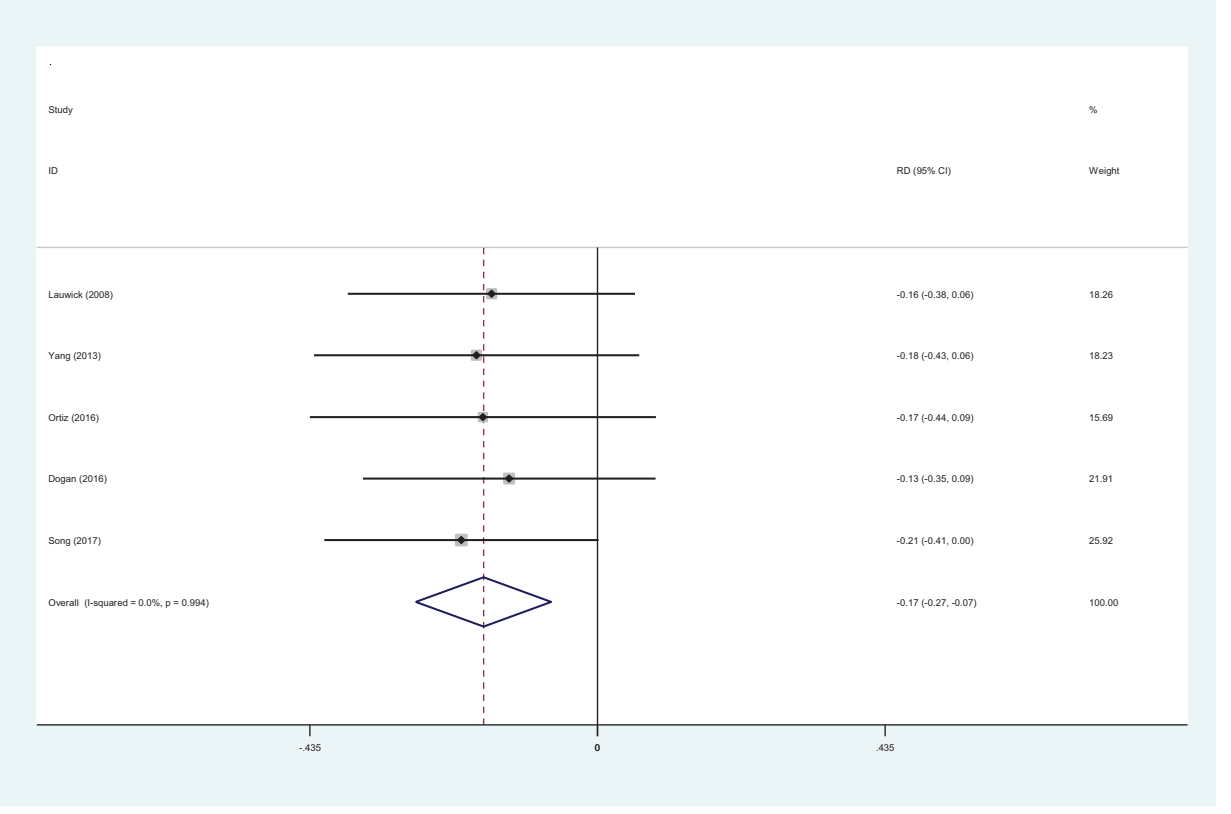


Figure 9. Forest plot diagram showing incidence of nausea and vomiting.

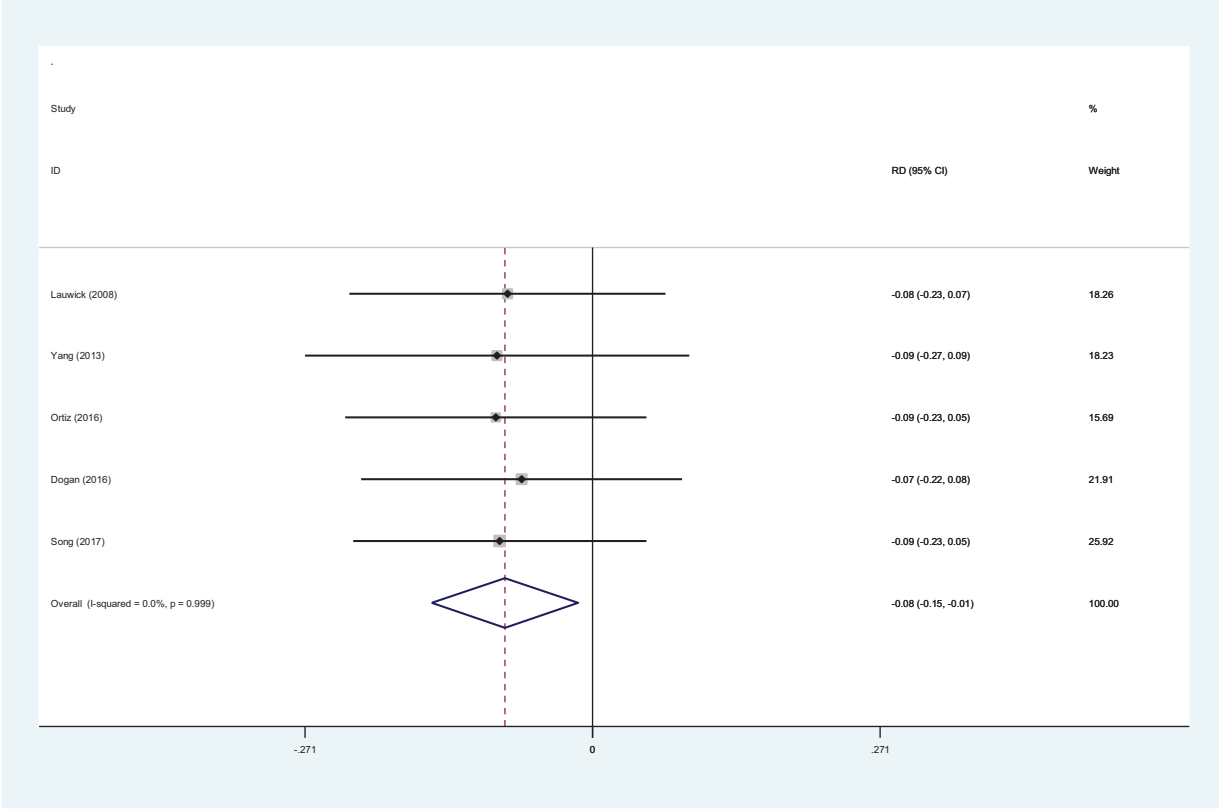


Figure 10. Forest plot diagram showing incidence of ileus.

ileus was found between the 2 groups (RD = −0.082, 95% CI: −0.151 to −0.014, $P = .019$; Fig. 10).

3.4.10. Pruritus. Five studies reported the postoperative complications of pruritus after LC. A fixed-effects model was used ($\chi^2 = 1.51$, df = 4, $I^2 = 0\%$, $P = .824$). The pooled results demonstrated that there was no significant difference between groups (RD = −0.070, 95% CI: −0.178 to 0.038, $P = .203$; Fig. 11).

3.4.11. Publication bias. Publication bias was evaluated by a funnel plot diagram. The funnel plot diagrams of VAS score and opioid consumption at 12 hours were symmetrical, indicating a low risk of publication bias (Figs. 12 and 13).

3.4.12. Quality of the evidence and recommendation strengths. The 2 outcomes in this meta-analysis were evaluated using the GRADE system. The evidence quality for each outcome was high which means further research was very unlikely to change our confidence in the estimate of effect (Table 4).

4. Discussion

To the best of our knowledge, this was the first meta-analysis to assess the efficiency and safety of intravenous infusion of lidocaine for pain management after LC. The most interesting finding of the present meta-analysis was that intravenous lidocaine can significantly reduce postoperative pain scores and opioid consumption after LC. In addition, there was a lower risk of opioid-related adverse effects in the lidocaine groups.

Although LC provides the possibility of minimal invasive and early discharge from hospital, postoperative pain still occurs in 50% to 70% of patients with moderate to severe.[17,18] Effective postoperative analgesia ensures rapid recovery and less postoperative complications. However, single-mode analgesia is insufficient to offer desired results and multimodal pain control following LC is recommended to reduce pain and opioid consumption. As a local anesthetic, lidocaine has been widely used in surgery through intravenous.[19] It was reported that lidocaine has the properties of analgesia and antihyperalgesia. Animal experiment and clinical trials have confirmed that the analgesic effect was achieved by blocking the sodium channel. In addition, lidocaine has also shown anti-inflammatory property.[20,21] Published articles have demonstrated that there were higher levels of inflammatory mediators in major abdominal surgery compared with less extensive operation.[22] Therefore, intravenous lidocaine was more preferable for reducing inflammation during surgery.

Some published articles have shown that intravenous lidocaine were effective in morphine-sparing management after abdominal surgery. Marret et al[23] reported that continuous intravenous administration of lidocaine during and after abdominal surgery improved patient rehabilitation and shortened hospital stay. In addition, there were fewer postoperative complications. McCarthy et al[24] showed that patients who received lidocaine infusion had lower pain scores, and decreased intraoperative anesthetic requirements, as well as faster return of bowel function and decreased length of hospital stay. However, the benefits of lidocaine for pain management in abdominal surgery remained controversial. Herroeder et al[25] found that there was no significant difference in postoperative pain ratings for patients

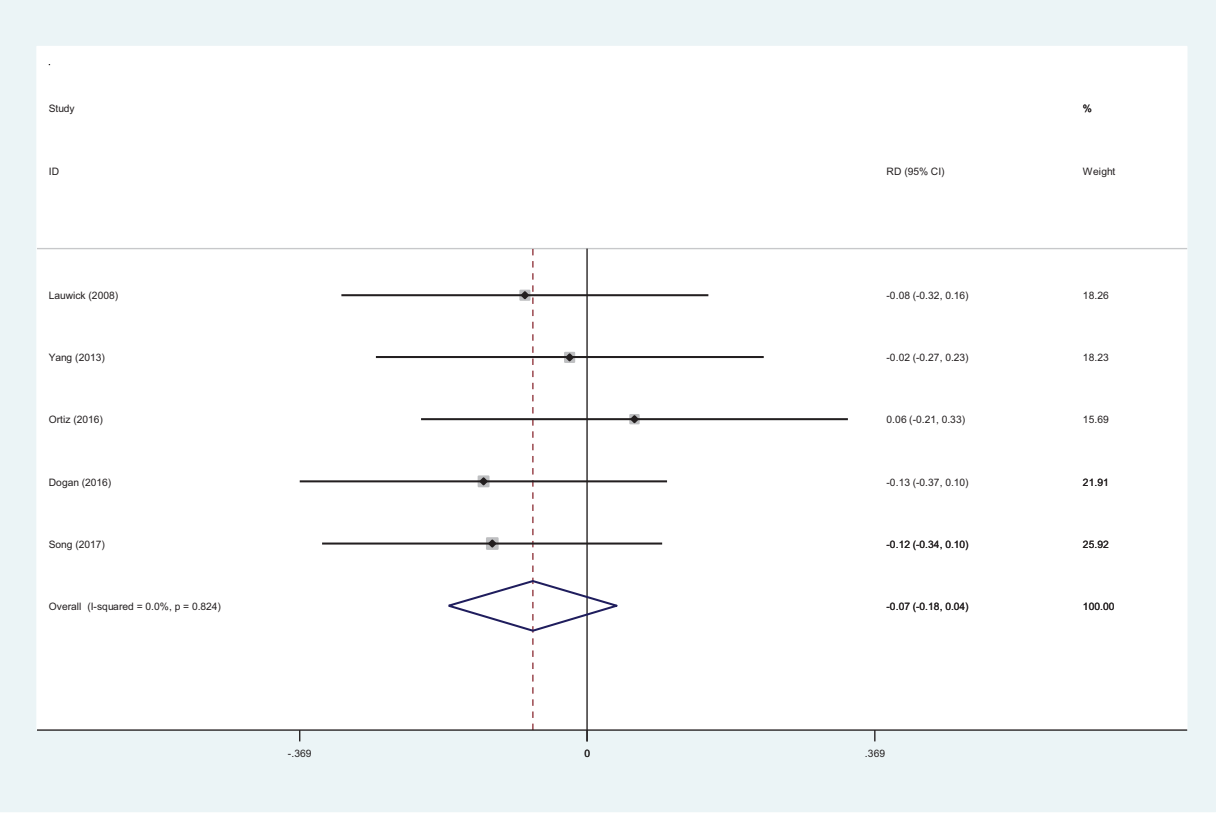


Figure 11. Forest plot diagram showing incidence of pruritus.

undergoing colorectal surgery. Based on the controversy above, we performed the present meta-analysis and indicated that intravenous lidocaine could significantly decrease the pain scores compared with saline groups. All included studies showed the initial dose of intravenous lidocaine is 1.5 mg/kg at the start of the procedure, thus we do not perform a dose–response analysis. Further investigation should explore the optimal dose for routine clinical practice. Several factors may influence the outcome of the study such as preoperative oral medication, other analgesics during surgery and various doses of lidocaine; however, only 5 studies were included in the study and it was insufficient to perform a subgroup analysis. More RCTs were needed in further investigation.

Opioid consumption was also an important indicator for assessing the analgesic effect of intravenous lidocaine. It was

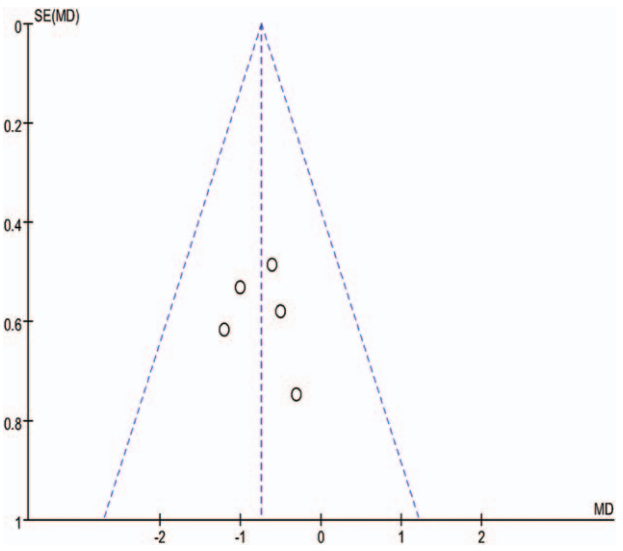


Figure 12. A funnel plot of pain scores at 12 hours after LC. LC = laparoscopic cholecystectomy.

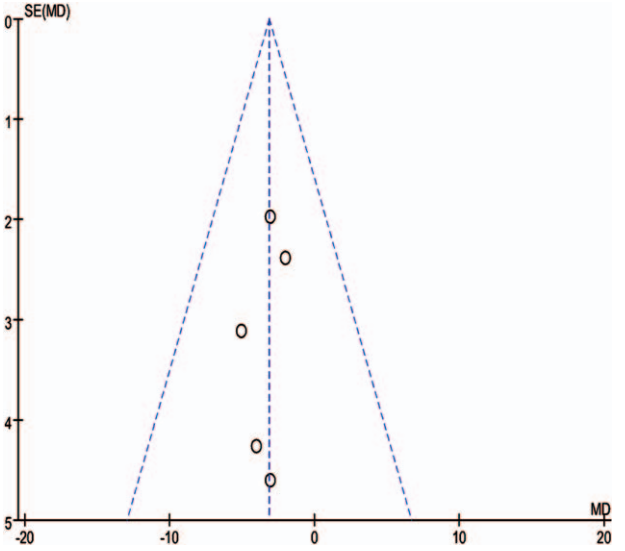


Figure 13. A funnel plot of opioid consumption at 12 hours after LC. LC = laparoscopic cholecystectomy.

Table 4

The GRADE evidence quality for main outcome.

Quality assessment							No of patients				
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Lidocaine groups	Control groups	Effect	Quality	Importance
VAS scores at 12 hours											
5	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	138	136	WMD = −0.743, 95% CI: −1.246 to −0.240	High	Critical
VAS scores at 24 hours											
5	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	138	136	WMD = −0.712, 95% CI: −1.239 to −0.184	High	Critical
VAS scores at 48 hours											
5	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	138	136	WMD = −0.600, 95% CI: −0.972 to −0.229	High	Critical
Opioid consumption at 12 hours											
5	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	138	136	WMD = −3.136, 95% CI: −5.591 to −0.680	High	Critical
Opioid consumption at 24 hours											
5	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	138	136	WMD = −4.739, 95% CI: −8.291 to −1.188	High	Critical
Opioid consumption at 48 hours											
5	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	138	136	WMD = −3.408, 95% CI: −5.489 to −1.326	High	Critical

GRADE = Grading of Recommendations Assessment, Development, and Evaluation , RCT = randomized controlled trial, VAS = visual analogy score, WMD = weighted mean difference.

usually used as adjunct to multimodal analgesia protocol. Also, the analgesic effect of the additional opioids provides a long postoperative period. Opioid consumption was also considered an objective method of measuring pain. However, opioid-related adverse effects, such as nausea, vomiting, headache, and respiratory depression, frequently occurred in previous articles.[26,27] In addition, massive opioid use may result in drug dependence which is a crucial issue that should be noted. Effective analgesia protocol contributes to less opioid consumption. Yardeni et al[28] performed a randomized, placebo-controlled study and showed that intravenous lidocaine could minimize postoperative opioid consumption and was associated with an attenuated suppression of a lymphocyte proliferative response and attenuated production of both proinflammatory and anti-inflammatory cytokines which provided improved pain control. Koppert et al[10] assumed that the main therapeutic effect of intravenous lidocaine after abdominal surgery with extended tissue damage can be attributed to a central antihyperalgesic effect mediated by mechanoinsensitive nociceptors, thus deceasing postoperative and narcotic consumption. Although a majority of studies have demonstrated that the intravenous lidocaine was associated with a opioid-sparing effect in major abdominal surgery, there was lack of reliable evidence in LC. Meta-analysis can strengthen statistical power and enlarger sample size by pooling results of published articles, which could point out stronger evidence. The present meta-analysis indicated that intravenous lidocaine could significantly reduce opioid consumption.

Postoperative complications were major concerns following additional opioids. Nausea and vomiting are well-known side effects which are related to systemic use of morphine. In our study, the overall incidence of nausea and vomiting was 25/138 in the lidocaine groups compared 48/ 136 in control groups ($P < .05$). Ileus was frequently occurred after general anesthesia following abdominal surgery which can delay recovery and cause unanticipated hospital admission. The present meta-analysis indicated that intravenous lidocaine was associated with a decreased risk of ileus following LC. Considering that only 5 studies were included in our study, large sample sizes of high-quality studies are, therefore, needed.

There are several potential limitations in the present meta-analysis: only 5 studies with small sample size were included, which may influence the results; some important data were insufficient such as functional outcome, making it difficult to analysis; considering that the small number of the included studies, sensitivity analysis was not performed; different dose of intravenous lidocaine used in the experimental groups may affect the results; (short duration of follow-up in the included studies may result in an underestimation of side effects.

Despite the limitations above, this study is the first meta-analysis from RCTs to illustrate the efficacy and safety of intravenous lidocaine for pain management after LC. High-quality RCTs with a large sample size are required to investigate the adequate analgesia protocol and potential adverse effects in future studies.

5. Conclusion

Intravenous lidocaine infusion significantly reduced postoperative pain scores and opioid consumption after LC. In addition, there were fewer adverse effects in the lidocaine groups. Higher quality RCTs are still required for further research.

Authors' contributions: FLL: conceived the design of the study. YLL, YMW, JLT, DYX, and JSZ performed and collected the data and contributed to the design of the study. JBZ finished the manuscript. All authors read and approved the final manuscript.

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