Systematic Review and Meta-Analysis

Medicine®

OPEN

# Pregabalin can decrease acute pain and morphine consumption in laparoscopic cholecystectomy patients

## A meta-analysis of randomized controlled trials

Shijie Li, MM[a], Junqiang Guo, MM[a], Fangjun Li, MM[a], Zhijia Yang, MM[a], Shuai Wang, MM[a], Changjiang Qin, MM[b,*]

**Abstract**

**Background:** Pregabalin has been used as an adjunct for the management of acute pain in laparoscopic cholecystectomy. This meta-analysis aimed to illustrate the efficacy and safety of pregabalin for pain management following laparoscopic cholecystectomy.

**Methods:** In March 2017, a systematic computer-based search was conducted in PubMed, EMBASE, Web of Science, Cochrane Database of Systematic Reviews, and Google databases. Data on patients prepared for laparoscopic cholecystectomy in studies that compared pregabalin versus placebo were retrieved. The primary endpoints were the visual analog scale (VAS) score with rest or mobilization at 6, 12, and 24 hours and total morphine consumption. The secondary outcomes were the morphine-related complications (i.e., nausea, vomiting, dizziness, somnolence, headache, pruritus, urine retention, respiratory depression, and blurred vision). Continuous outcomes were expressed as the weighted mean difference (WMD) with a corresponding 95% confidence interval (CI), and discontinuous outcomes were expressed as a risk ratio (RR) with a corresponding 95% CI.

**Results:** Twelve clinical studies with 938 patients (gabapentin group = 536, control group = 402) were ultimately included in the meta-analysis. Pregabalin was associated with reduced pain scores with rest at 6, 12, and 24 hours, which corresponded to a reduction of 11.27 points at 6 hours, 9.46 points at 12 hours, and 3.99 points at 24 hours on a 100-point VAS. Moreover, pregabalin was associated with reduced pain scores with mobilization at 6, 12, and 24 hours, which corresponded to a reduction of 8.74 points, 5.80 points and 6.37 points at 6, 12, and 24 hours, respectively, on a 110-point VAS. Furthermore, pregabalin reduced the occurrence of nausea and vomiting. There were no significant differences in the occurrence of respiratory depression, pruritus, dizziness, blurred vision, and headache.

**Conclusions:** Pregabalin was efficacious in the reduction of postoperative pain, total morphine consumption, and morphine-related complications following laparoscopic cholecystectomy. In addition, a high dose of pregabalin was more effective than a low dose. The dose of pregabalin differed across the studies, and the heterogeneity was large. More studies are needed to verify the optimal dose of pregabalin in laparoscopic cholecystectomy patients.

**Abbreviations:** CI = confidence interval, RR = risk ratio, NNH = number needed to harm, NNT = number need to treat, NRS = numerical rating scale, PRISMA = preferred reporting items for systematic reviews and meta-analyses, RCTs = randomized controlled trials, SD = standard deviation, VAS = visual analog scale, WMD = weighted mean differences.

**Keywords:** laparoscopic cholecystectomy, meta-analysis, pregabalin

## 1. Introduction

Laparoscopic cholecystectomy is one of the most common surgical procedures; however, pain after this surgery remains a major challenge.[1,2] Previous reports revealed that approximately 80% of patients undergoing laparoscopic cholecystectomy experienced moderate to extreme postoperative pain.[3,4] Pain after surgery was associated with several complications including prolonged wound healing, increased infections, and added costs.[5] Intense acute pain after laparoscopic cholecystectomy might predict the development of chronic pain.[6] To achieve effective postoperative pain relief, multimodal therapy with 2 or more analgesics and modalities that work by different mechanisms to improve analgesia and reduce the severity of adverse effects are becoming increasingly popular.[7] Opioids are the first alternative for treating moderate to severe postoperative pain, but their use is limited due to adverse effects such as nausea, vomiting, pruritus, and urinary retention.[8–10] For surgery, operatively

*Editor: Kazuo Hanaoka.*

*SJL and JQG contributed equally to this article and should be listed as co-first author.*

*The authors have no conflicts of interest to disclose.*

*[a] Department of Trauma Emergency, [b] Department of General Surgery, Huaihe Hospital, Henan University, Kaifeng, China.*

*[*] Correspondence: Changjiang Qin, Department of General Surgery, Huaihe Hospital, Henan University, Kaifeng, China (e-mail: zhaoyongqiang09@126.com).*



*Medicine (2017) 96:21(e6982)*

*Received: 23 March 2017 / Received in final form: 25 April 2017 / Accepted: 26 April 2017*

*http://dx.doi.org/10.1097/MD.0000000000006982*

induced neuroplastic changes may provoke sensitization and cause postoperative hyperalgesia or allodynia. Therefore, an optimal multimodal analgesic regimen, including antihyperalgesic drugs to attenuate central sensitization, may have beneficial effects for pain control after surgery.

Pregabalin is an anticonvulsant agent that has been widely used preoperatively in different types of surgeries (total knee arthroplasty, total hip arthroplasty, spinal surgery, and nasal surgery) to relieve postoperative pain.[11–14] It acts in synergy with morphine and has a preemptive effect as well.[15] Several randomized controlled trials (RCT) have compared pregabalin with control groups in laparoscopic cholecystectomy cases. Many of these trials contained relatively small samples and demonstrated inconsistent outcomes.[16,17] A previous meta-analysis compared pregabalin versus placebo for acute pain control in patients who underwent different surgical procedures.[18] However, the disadvantages were as follows: the pain in each surgical category was different, and thus a large heterogeneity may have existed, which influenced the final results; (2) complications of using pregabalin were not compared; and (3) different doses of gabapentin were not compared. Additionally, more evidence is emerging, and it is necessary to re-evaluate the efficacy and safety of pregabalin for pain control after laparoscopic cholecystectomy. This meta-analysis aimed to evaluate whether pregabalin can decrease pain intensity, total morphine consumption, and related complications, and whether high-dose pregabalin is superior to low-dose pregabalin.

## 2. Materials and methods

This systematic review was reported according to the preferred reporting items for systematic reviews and meta-analyses guidelines.[19]

### 2.1. Search strategies

The following databases were searched in March 2017 without restrictions on location: PubMed (1950–March 2017), EMBASE (1974–March 2017), the Cochrane Library (March 2017 Issue 3), and the Google database (1950–March 2017). The Mesh terms and their combinations used in the search were as follows: "laparoscopic cholecystectomy" OR "Cholecystectomy, Laparoscopic"[Mesh] AND "Pregabalin" OR "Pregabalin"[Mesh]. Only articles originally written in English or translated into English and full-length articles were considered. Identified references were screened using the title, abstract, and keywords. Searches of the reference lists of identified studies were also conducted. This meta-analysis collected data from published articles; thus, no ethical approval was necessary.

### 2.2. Inclusion criteria and study selection

We determined the inclusion criteria in accordance with the PICOS principle. Participants (P): patients who were prepared for laparoscopic cholecystectomy due to cholecystitis; Intervention (I): perioperative oral pregabalin was used as an adjunct to multimodal anesthetics as an intervention group; Comparison (C): placebo; Outcomes (O): visual analog scale (VAS score at 6, 12, and 24 hours, total morphine consumption and related complications (nausea, vomiting, dizziness, somnolence, headache, pruritus, urinary retention, respiratory depression, and blurred vision); Study design (S): RCTs. Two independent reviewers screened the title and abstracts of the identified studies after removing the duplicates from the search results. Any disagreements about the inclusion or exclusion of a study were resolved by discussion or consultation with an expert. The reliability of the study selection was determined by Cohen's kappa test, and the acceptable threshold value was set at 0.61.[20,21]

### 2.3. Data abstraction and quality assessment

A specific extraction was conducted to collect data in a pregenerated standard Microsoft Excel (Microsoft Corporation, Redmond, WA) file. The items extracted from relevant studies were as follows: first author and publication year, country, sample size of the intervention and control groups, surgery type, preoperative and postoperative doses, timing and frequency, and the total dose of pregabalin per number of days and follow-ups. Outcomes such as the VAS score at 6, 12, and 24 hours, total morphine consumption, and morphine-related complications (nausea, vomiting, dizziness, somnolence, headache, pruritus, urinary retention, respiratory depression, and blurred vision) were abstracted and recorded on a spreadsheet. Postoperative pain intensity was measured using a 110-point VAS (0 = no pain and 100 = extreme pain). When the numerical rating scale was reported, it was converted to a VAS. Additionally, a 10-point VAS was converted to a 110-point VAS.[22] Data in other forms (i.e., median, interquartile range, and mean ± 95% confidence interval (CI)) were converted to the mean ± standard deviation (SD) according to the Cochrane Handbook.[23] If the data were not reported numerically, we extracted these data using t "GetData Graph Digitizer" software from the published figures. All the data were extracted by 2 independent reviewers, and disagreements were resolved by discussion.

The quality of all included trials was independently assessed by 2 reviewers on the basis of the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0 (http://handbook.cochrane.org/).[23] A total of 7 domains were used to assess the overall quality as follows: random sequence generation, allocation concealment, blinding of participant and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each domain was measured and classified as low bias, unclear bias, or high bias. We used Review Manager 5.3.0 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) to graph the risk of bias summary and the risk of bias graph.

### 2.4. Outcome measures and statistical analysis

Continuous outcomes (VAS score with rest or mobilization at 6, 1, and 24 hours and total morphine consumption) were expressed as the weighted mean differences (WMD) with 95% CI. Dichotomous outcomes (the occurrence of nausea, vomiting, dizziness, somnolence, headache, pruritus, urinary retention, respiratory depression, and blurred vision) were expressed as a risk ratio (RR) with 95% CI. Statistical significance was set at $P < .05$ to summarize the findings across the trials. Variables in the meta-analysis were calculated using Stata software, version 12.0 (Stata Corp., College Station, TX). Statistical heterogeneity was evaluated using the $\chi^2$ test and the $I^2$ statistic. We used the random-effect model to summarize the final outcome due to the different doses of pregabalin used in the studies. Publication bias was tested using funnel plots and Begg's test. We considered that no publication bias occurred if the effect size in the funnel plot was symmetrical, and the $P$-value in Begg's test was $> .05$.

Subgroup analysis was conducted according to the dose of pregabalin (<300 mg/d or ≥300 mg/d). In addition, we calculated the number needed to harm (NNH) and the number needed to treat (NNT) to examine the risks (i.e., regarding complications) compared to the benefits of gabapentin therapy.[24] The relationship between gabapentin dosage and the VAS score with rest at 6, 12, and 24 hours was explored using GraphPad Prism software (Version 6.0; GraphPad Software, San Diego, CA). The correlation coefficient (r) was used to evaluate the relationship between the dosage of gabapentin and the VAS score with rest at 6, 12, and 24 hours. We did not explore the relationship between the pregabalin dose and the VAS score with mobilization at 6, 12, and 24 hours because the included number of studies was relatively small.

## 3. Results

### 3.1. Search results and quality assessment

In the initial search, a total of 505 studies were identified from the electronic databases (PubMed = 155, Embase = 123, Web of Science = 58, Cochrane Library = 85, and Google database = 114). All papers were input into Endnote X7 (Thompson Reuters, CA, USA) software for the removal of duplicate papers. A total of 203 papers were reviewed, and 191 papers were removed according to the inclusion criteria at abstract and title levels. Ultimately, 12 clinical studies with 938 patients (gabapentin group = 536, control group = 402) were included in the meta-analysis.[16,17,25–34] The flow diagram for the included studies can be seen in Fig. 1. Two studies administered 2 different doses of pregabalin (150 mg/d and 300 mg/d) versus placebo,[26,29] and the studies were divided into 2 arms.[35] One study adopted 2 different pregabalin doses (75 mg/d and 150 mg/d), and this study was also divided into 2 arms.[17] One study adopted 2 different pregabalin doses (100 mg/d and 150 mg/d), and this study was also divided into 2 arms.[16] The general characteristics of the included studies can be seen in Table 1.

The risk of bias graph and the risk of bias summary are shown in Fig. 2A and B, respectively. Only 2 studies did not describe the random-sequence generation procedure;[29,30] the remaining 10 clinical trials performed appropriate random sequence generation. Two studies did not describe allocation concealment.[30,32] In addition, the risks of bias for blinding to the outcome assessment were unclear in 2 studies.[29,30] Thus, the overall quality of the included RCTs were high. The overall kappa value regarding the evaluation of the risk of bias of included RCTs was 0.815, which indicates that the agreement between the 2 reviewers was acceptable.

### 3.2. Results of the meta-analysis

**3.2.1. VAS scores with rest at 6, 12, and 24 hours.** Postoperative VAS scores with rest at 12 hours were reported

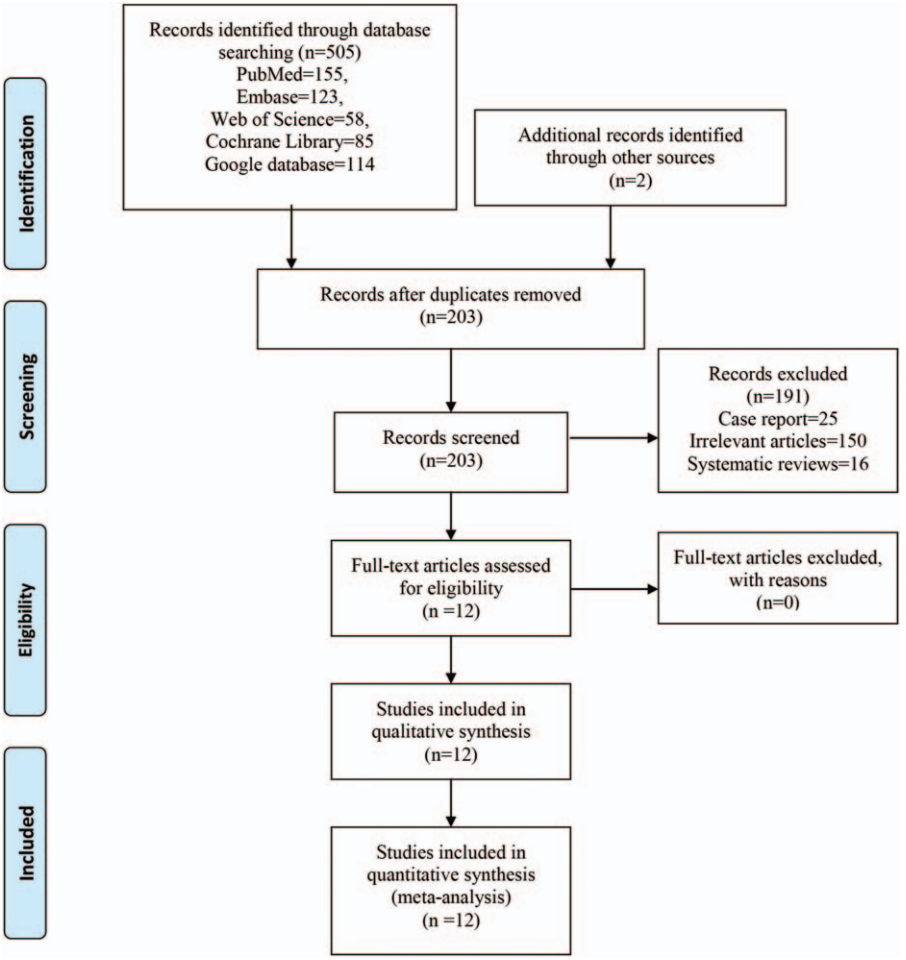


**Figure 1.** Flowchart of study search and inclusion criteria.

**Table 1**

**The general characteristics of the included studies.**

| Study | Country | Control group | Surgery | Intervention group | | | | Outcomes | Follow-up |
|---|---|---|---|---|---|---|---|---|---|
| | | | | No. of patients | Preoperative | Postoperative | Total dose, mg/d | | |
| Agarwal et al[25] | India | Placebo (n=30) | Laparoscopic cholecystectomy | 30 | Pregabalin 150 mg a day 1 h before surgery. | No | 150 | 2, 3, 4,7,8 | 6 mo |
| Balaban et al[26] | Turkey | Placebo (n=30) | Laparoscopic cholecystectomy | 30 | Arm1=Pregabalin 150 mg 1 h before surgery | No | 150 | 3, 4, 6 | 24 h |
| | | | Laparoscopic cholecystectomy | 30 | Arm2=Pregabalin 300 mg 1 h before surgery | No | 300 | | 24 h |
| Bekawi et al[27] | Egypt | Placebo (n=30) | Laparoscopic cholecystectomy | 30 | Pregabalin 150 mg single dose 2 h preop, 12 h postoperatively for 2 d | No | 300 | 1, 2, 3, 5, 6 | 3 mo |
| Chang et al[28] | South Korea | Placebo (n=38) | Laparoscopic cholecystectomy | 39 | Pregabalin 150 mg 2 dose 1 h before inducing anesthesia | Pregabalin 150 mg 12 h after first dose with sips of water | 300 | 1, 2, 3, 5, 6 | 1 y |
| Esmat and Farag[29] | Egypt | Paracetamol (n=25) | Laparoscopic cholecystectomy | Arm1 (25) | Pregabalin 150 mg single dose 2 h before inducing anesthesia | No | 150 | 4,10,12 | 48 h |
| | | | | Arm2 (25) | Pregabalin 300 mg single dose 2 h before inducing anesthesia | No | 300 | | |
| Gupta et al[30] | India | Placebo (n=60) | Laparoscopic cholecystectomy | 60 | Pregabalin 150 mg single dose 75–90 min before inducing anesthesia | No | 150 | 1,2,3,4,5,6,9,10,12,16 | 48 h |
| Gurunathan et al[31] | Australia | Placebo (n=25) | Laparoscopic cholecystectomy | 25 | Pregabalin 150 mg single dose1 h preop | No | 150 | 1, 3, 4, 5, 6 | 24 h |
| Jokela et al[17] | Finland | Diazepam 5 mg (n=28) | Laparoscopic cholecystectomy | Arm1 (30) | Arm1=Pregabalin 75 mg single dose1 h preop | No | 75 | 1,2,3,4,5,6,9,10,12,16 | 72 h |
| | | | | Arm2 (26) | Arm2=Pregabalin 150 mg single dose1 h preop | No | 150 | 1,2,3,4,5,8,9,10,14,15,16 | 3 mo |
| Mishra et al[32] | India | Placebo (n=30) | Laparoscopic cholecystectomy | n30 | Pregabalin 150 mg single dose 1 h before inducing anesthesia | No | 150 | 6,7,8,10,12,13,16 | 1 mo |
| Parveen et al[33] | India | Clonidine 0.3 mg (n=40) | Laparoscopic cholecystectomy | n40 | Pregabalin 150 mg single dose 1 h preop | No | 150 | 1,2,3,4,5,6,9,10,12,13 | 1 wk |
| Peng et al[16] | Canada | Placebo (n=46) | Laparoscopic cholecystectomy | Arm1 (48) | Arm1=Pregabalin 50 mg, 1 h before surgery | Every 12 h after operation for a total of 3 doses | 100 | 1,2,3,4,5,6,9,10,12,14 | 72 h |
| | | | | Arm2 (48) | Arm2=Pregabalin 75 mg 1 h before surgery | Every 12 h after operation for a total of 3 doses | 150 | 1,2,3,5,6,9,10,11,12 | 72 h |
| Sarakatsianou et al[34] | USA | Placebo (n=20) | Laparoscopic cholecystectomy | 20 | Pregabalin 300 mg the night before surgery and 1 h before surgery | No | 600 | 1,2,3,9,10,12 | 24 h |

h=hours, mo=month; preop=preoperative; postop=postoperative; 1=VAS with rest at 6 h, 2=VAS with rest at 12 h; 3=VAS with rest at 24 h; 4=VAS with mobilization at 6 h, 5=VAS with mobilization at 12 h, 6=VAS with mobilization at 24 h, 7=total morphine consumption; 8=the occurrence of nausea; 9=the occurrence of vomiting; 10=the occurrence of pruritus. 11=the occurrence of respiratory depression, 12=the occurrence of pruritus, 13=the occurrence of dizziness,14=the occurrence of blurred vision, 16=the occurrence of headache, wk=week.

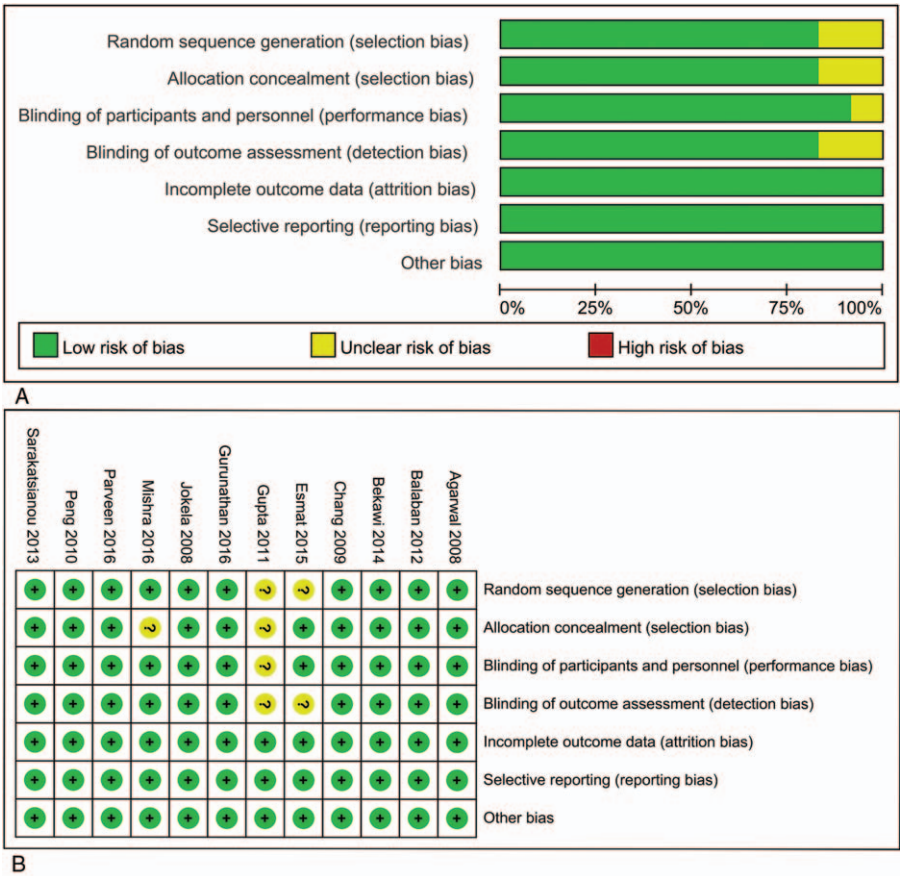


**Figure 2.** (A) The risk of bias graph. (B) Risk of bias summary of included randomized controlled trials. +, no bias; −, bias; ?, bias unknown.

in 3 studies, and the pooled results indicated that the preoperative administration of pregabalin can decrease the VAS score with rest at 6 hours (WMD = −11.27, 95% CI −16.92, −5.62, $P = .000$, Fig. 3). The postoperative VAS scores at 12 hours in the included studies had a large heterogeneity ($I^2 = 96.4\%$, $P = .000$), which required a random-effect model that was performed to analyze the data. Funnel plots (Fig. 4 A) and Begg's tests (Fig. 4B $P = .722$) were performed, and the results indicated that there was no

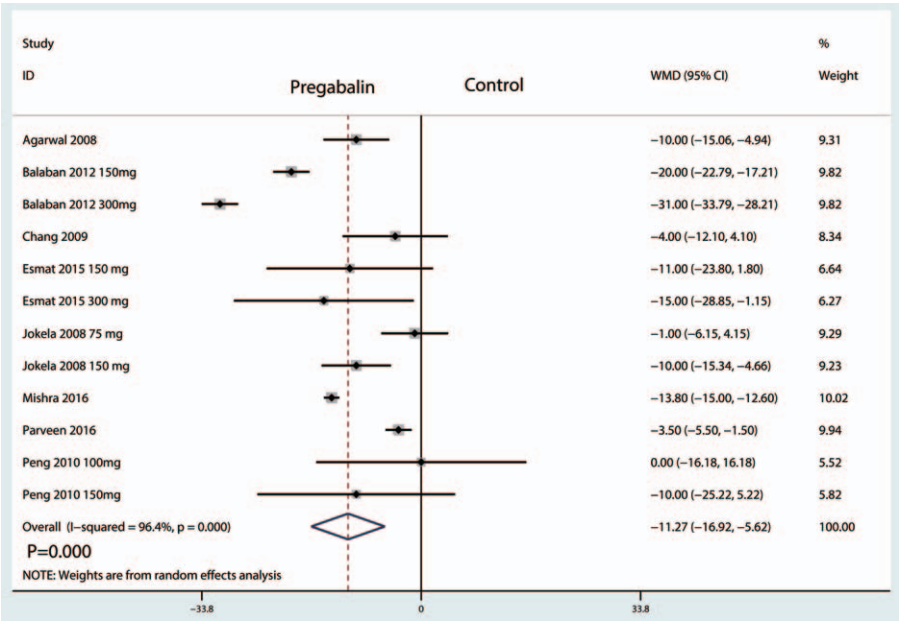


**Figure 3.** Forest plots of the included studies comparing the VAS with rest at 6 hours. VAS = visual analog scale.

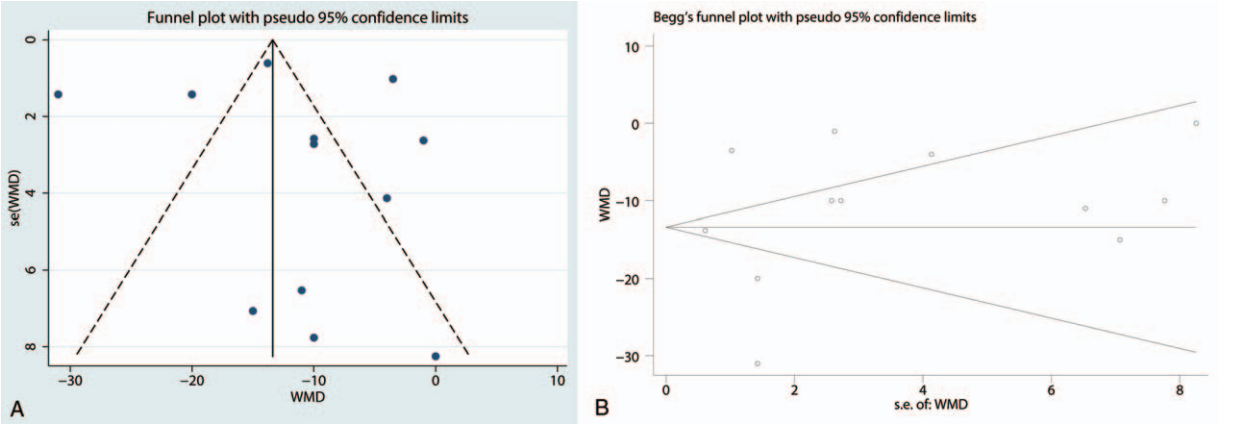


**Figure 4.** (A) Funnel plot of VAS with rest at 6 hours. (B) Begg's test of VAS with rest at 6 hours. VAS = visual analog scale.

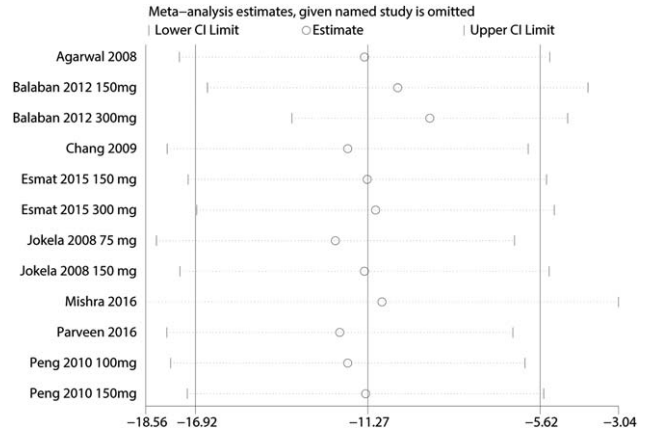


**Figure 5.** Sensitivity analysis of the VAS with rest at 6 hours. VAS = visual analog scale.

publication bias between the included studies in terms of the VAS score at 6 hours. A sensitivity analysis was then conducted to analyze the source of heterogeneity between the studies, and the results indicated that none of the included studies affected the final results (Fig. 5).

The meta-analysis results indicated that gabapentin can decrease VAS scores at 12 hours (WMD = −9.46, 95% CI −18.13, −0.79, $P = .032$, Fig. 6). Postoperative VAS scores at 12 hours in the included studies had a large heterogeneity ($I^2 = 98.3\%$, $P = .000$), which required a random-effect model to be performed to analyze the relevant data.

The meta-analysis results indicated that gabapentin can decrease VAS scores at 24 hours (WMD = −3.99, 95% CI −6.80, −1.19, $P = .005$, Fig. 7). Postoperative VAS scores at 24 hours in the included studies had a large heterogeneity ($I^2 = 67.3\%$, $P = .003$), which required a random-effect model to be performed to analyze the relevant data.

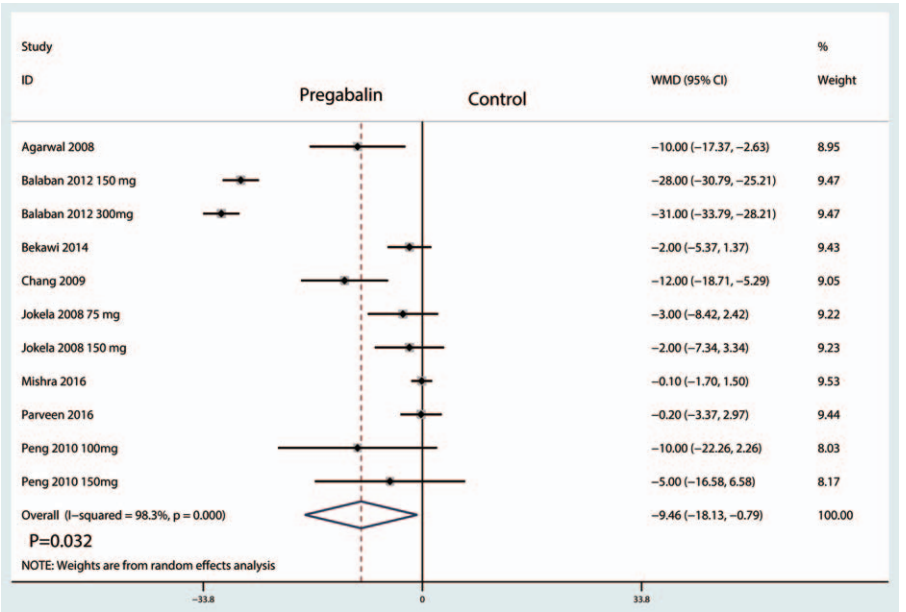


**Figure 6.** Forest plots of the included studies comparing the VAS with rest at 12 hours. VAS = visual analog scale.

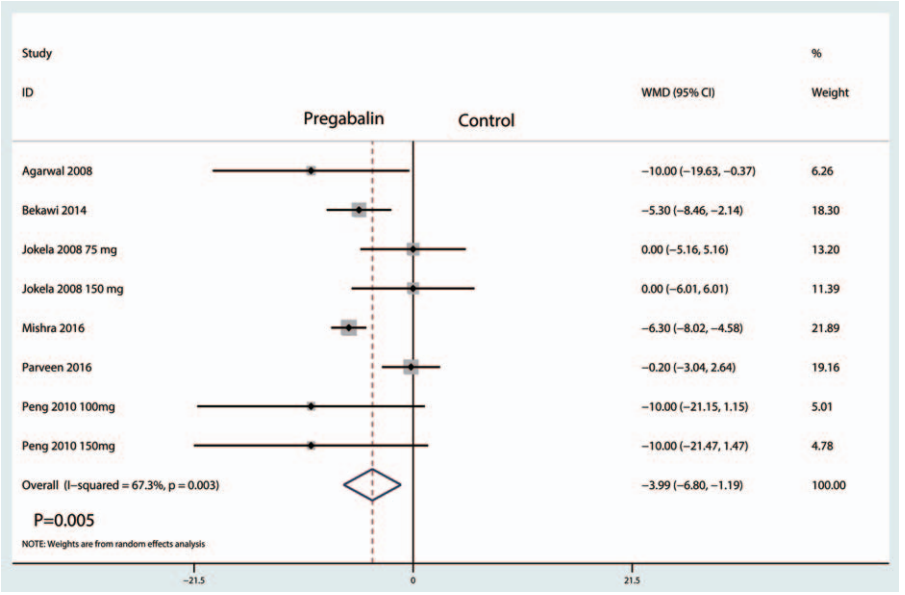


**Figure 7.** Forest plots of the included studies comparing the VAS with rest at 24 hours. VAS = visual analog scale.

***3.2.2. VAS scores with mobilization at 6, 12, and 24 hours.*** Postoperative VAS scores with mobilization at 12 hours were reported in 3 studies, and the pooled results indicated that the preoperative administration of pregabalin can decrease the VAS score with mobilization at 6 hours (WMD = −8.74, 95% CI −13.07, −4.42, $P = .000$, Fig. 8). The postoperative VAS scores with mobilization at 6 hours in the included studies had a large heterogeneity ($I^2 = 34.1\%$, $P = .000$), which required a random-effect model to be performed to analyze the data.

The meta-analysis results indicated that pregabalin can decrease the VAS score with mobilization at 12 hours (WMD = −5.80, 95% CI −10.26, −1.35, $P = .011$, Fig. 9). Postoperative VAS with mobilization at 12 hours in the included studies had a large heterogeneity ($I^2 = 43.4\%$, $P = .171$), which required a random-effect model to be performed to analyze the relevant data.

The meta-analysis results indicated that pregabalin can decrease the VAS score with mobilization at 24 hours (WMD = −6.37, 95% CI −11.80, −0.94, $P = .021$, Fig. 10). The postoperative VAS scores with mobilization at 24 hours in the included studies had a large heterogeneity ($I^2 = 59.0\%$, $P = .087$), which required a random-effect model to be performed to analyze the relevant data.

***3.2.3. Dose–effect relationship.*** We plotted the pregabalin dose on the abscissa and the corresponding VAS score with rest at 6, 12, and 24 hours on the ordinate to generate a scatterplot. In addition, the linear correlation coefficient ($r$) was calculated.

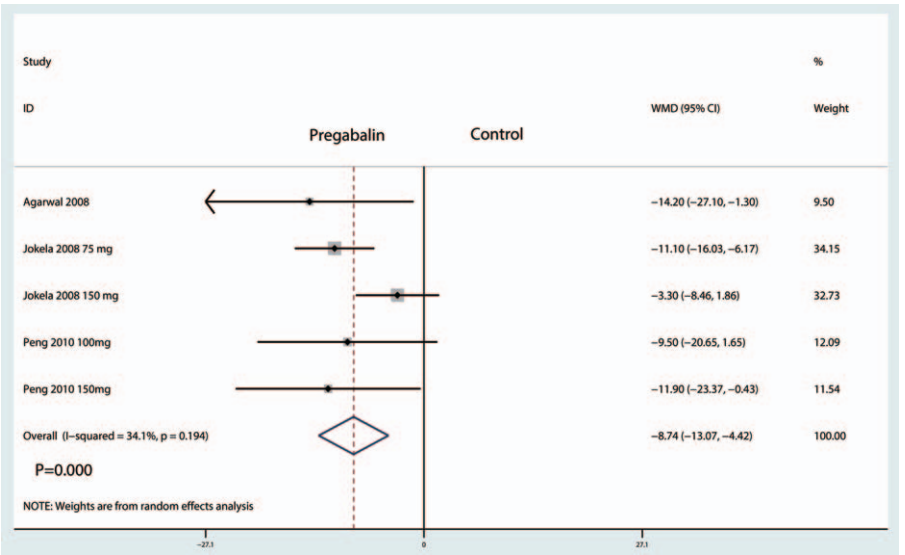


**Figure 8.** Forest plots of the included studies comparing the VAS with mobilization at 6 hours. VAS = visual analog scale.

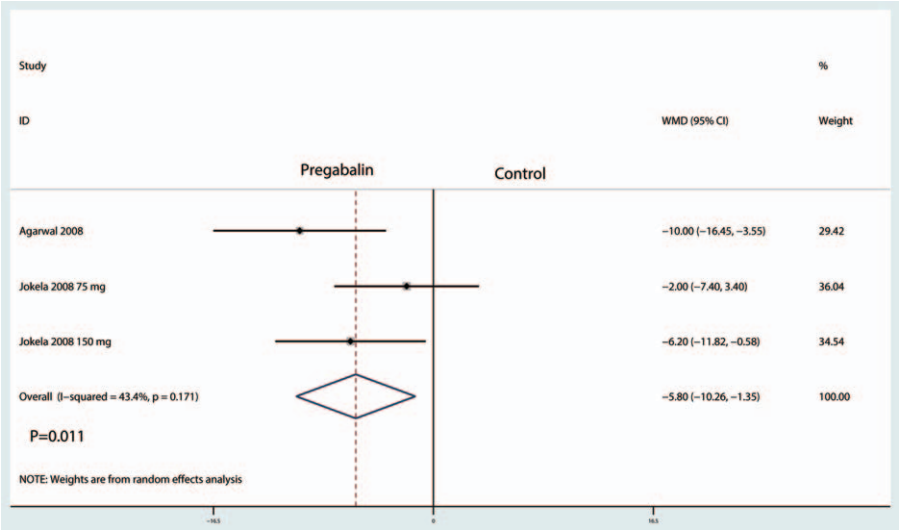


**Figure 9.** Forest plots of the included studies comparing the VAS with mobilization at 12 hours. VAS = visual analog scale.

There was a negative correlation between the dosage of pregabalin and the VAS score at 6 hours ($r=-0.623$, $P=.031$; Fig. 11A). There was no correlation between the dosage of pregabalin and the VAS score with rest at 12 hours ($r=-0.437$, $P=.139$; Fig. 11B) and 24 hours ($r=-0.496$, $P=.211$; Fig. 11C).

***3.2.4. Total morphine consumption.*** Total morphine consumption was presented in 6 studies. One study adopted 4 different doses of gabapentin compared to a placebo and was consequently divided into 4 groups. The pooled results indicated that gabapentin can reduce total morphine consumption (WMD $=-168.60$, 95% CI $-231.78$, $-105.42$, $P=.000$, Fig. 12).

***3.2.5. Complications.*** There were no significant differences between the groups in the occurrence of nausea (RR = 0.60, 95% CI 0.42, 0.88, $P=.157$, NNT = 8.32, Fig. 13A), vomiting (RR = 0.56, 95% CI 0.35, 0.90, $P=.017$, NNT = 8.02, Fig. 13B), respiratory depression (RR = 0.71, 95% CI 0.17, 3.02, $P=.647$, NNT = 41.66, Fig. 13C), pruritus (RR = 1.16, 95% CI 0.30, 4.52, $P=.835$, NNH = 45.3, Fig. 13D), dizziness (RR = 1.61, 95% CI 0.76, 3.38, $P=.212$, Fig. 13E, NNH = 4.61), blurred vision (RR = 0.85, 95% CI 0.16, 4.57, $P=.853$, Fig. 13F, NNT = 13.5), or headache (RR = 1.01, 95% CI 0.74, 1.38, $P=.959$, Fig. 14, NNT = 190.88).

***3.2.6. Subgroup analyses.*** Subgroup analyses were conducted according to a low dose (<300 mg/d) and a high dose of gabapentin (≥300 mg/d). The detailed results can be seen in Table 2. The pooled results indicated that a high dose of gabapentin can reduce the VAS score with rest at 6, 12, and 24 hours and nausea and vomiting compared to a low dose ($P<.05$). The other outcomes were all associated with a low dose of gabapentin; thus, the data were insufficient to perform the subgroup analyses.

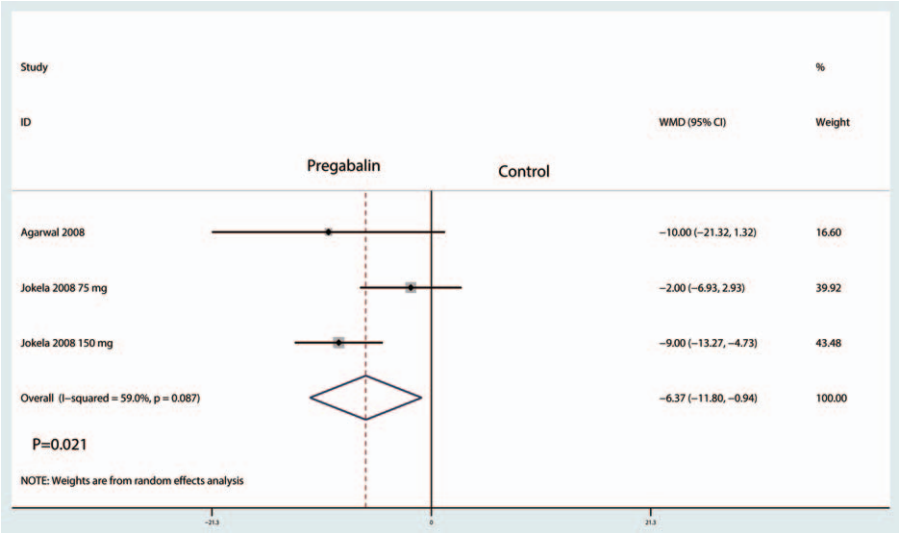


**Figure 10.** Forest plots of the included studies comparing the VAS with mobilization at 24 hours. VAS = visual analog scale.

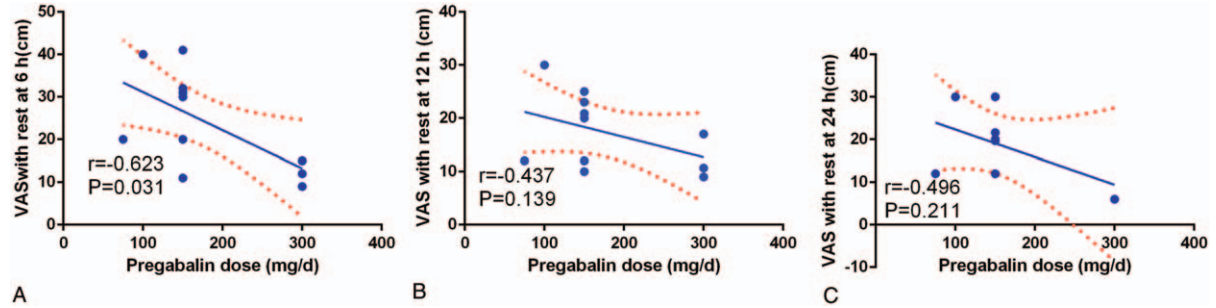


**Figure 11.** (A) Scatter plot showing the relationship between the dose of pregabalin and the VAS with rest at 6 hours; (B) scatter plot showing the relationship between the dose of pregabalin and the VAS at 12 hours; (C) scatter plot showing the relationship between the dose of pregabalin and the VAS at 24 hours. VAS = visual analog scale.

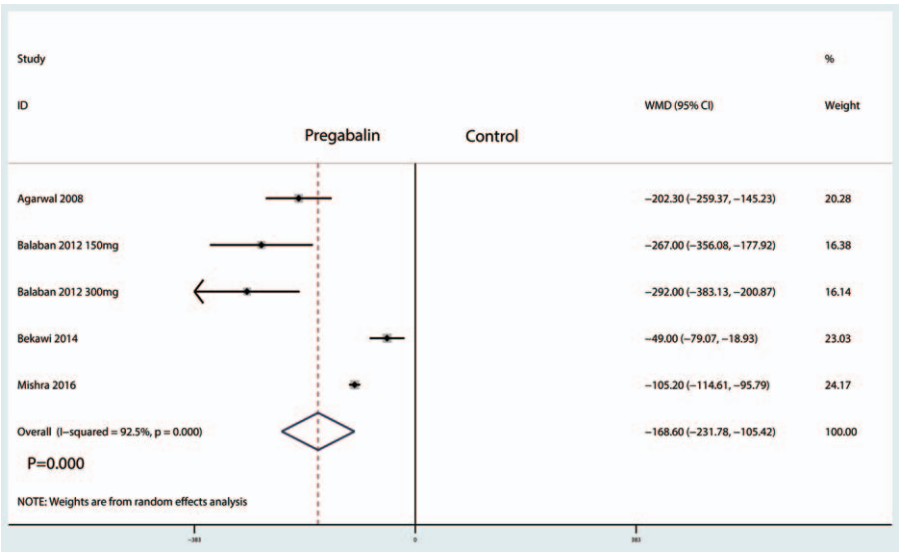


**Figure 12.** Forest plots of the included studies comparing the total morphine consumption.

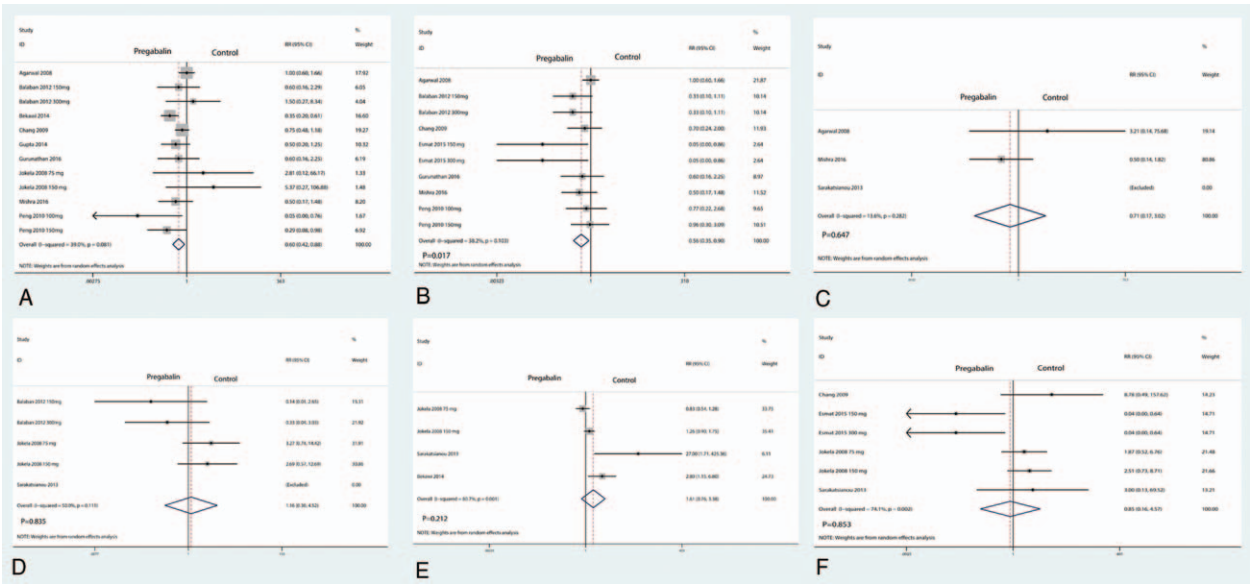


**Figure 13.** Forest plots of the included studies comparing the occurrence of, (A) nausea; (B) vomiting; (C) respiratory depression; (D) pruritus; (E) dizziness; (F) blurred vision.

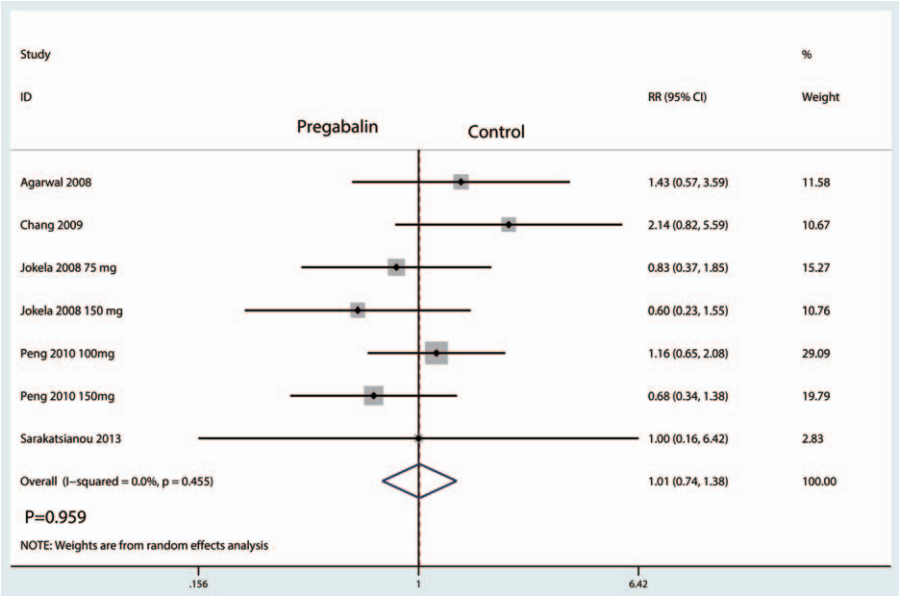


**Figure 14.** Forest plots of the included studies comparing the occurrence of headache.

## 4. Discussion

This is the first meta-analysis that examined the preoperative administration of oral pregabalin for pain control in patients following laparoscopic cholecystectomy. Pooled results indicated that preoperatively administered oral pregabalin was associated with reduced pain scores at 6, 12, and 24 hours with rest, which was equivalent on a 110-point VAS to 11.27 points at 6 hours, 9.46 points at 12 hours, and 3.99 points at 24 hours with rest. Meanwhile, preoperatively administered oral pregabalin was associated with a significant reduction in pain scores at 6, 12, and 24 hours with mobilization, which was equivalent on a 110-point VAS to 8.74 points at 6 hours, 5.80 points at 12 hours, and 6.37 points at 24 hours with mobilization. The dose–effect relationship indicated that the VAS scores with rest at 6, 12, and 24 hours tended to decrease as the pregabalin dose increased. The cumulative total morphine consumption was also reduced in the pregabalin group. The most important finding of this meta-analysis was that pregabalin can reduce the occurrence of nausea and vomiting after laparoscopic cholecystectomy, and high-dose pregabalin is superior to low-dose pregabalin. There were no significant differences in the occurrences of respiratory depression, pruritus, dizziness, blurred vision, and headache.

A major strength of this study is the comprehensive search with strict statistical calculations. Another strength is that we examined the dose–effect relationship between the dose of

**Table 2**

**Subgroup analysis for the VAS with rest at 6, 12, and 24 hours, total morphine consumption, and the occurrence of nausea and vomiting.**

| | | | | Incidence | | | |
|---|---|---|---|---|---|---|---|
| Variables | Studies (n) | Patients (n) | *P*-value | Weighted mean difference/ risk ratio (95% CI) | Heterogeneity *P*-value ($I^2$) | Model | Subgroup difference |
| VAS with rest at 6 h | | | | | | | |
| High dose | 3 | 160 | .000 | −16.98 (−36.72, −3.85) | .000, 95.2 | Random | 0.000 |
| Low dose | 9 | 451 | .002 | −9.39 (−14.34, −4.44) | .000, 93.8 | Random | |
| VAS with rest at 12 h | | | | | | | |
| High dose | 3 | 326 | .013 | −15.04 (−35.74, −5.66) | .000, 98.8 | Random | 0.011 |
| Low dose | 8 | 550 | .035 | −7.28 (−16.58, −2.02) | .000, 97.7 | Random | |
| VAS with rest at 24 h | | | | | | | |
| High dose | 2 | 251 | .010 | −5.30 (−8.46, −2.14) | .562, 0.0 | Fixed | 0.031 |
| Low dose | 6 | 480 | .010 | −3.84 (−7.35, −0.33) | .002, 71.6 | Random | |
| Total morphine consumption | | | | | | | |
| High dose | 2 | 215 | .000 | −166.54 (−404.54, −71.47) | .000, 95.9 | Random | 0.025 |
| Low dose | 3 | 261 | .002 | −131.66 (−318.51, −61.33) | .000, 91.3 | Random | |
| The occurrence of nausea | | | | | | | |
| High dose | 3 | 344 | .001 | 0.57 (0.41, 0.80) | .058, 64.9 | Random | 0.000 |
| Low dose | 9 | 582 | .002 | 0.57 (0.40, 0.81) | .137, 35.1 | Fixed | |
| The occurrence of vomiting | | | | | | | |
| High dose | 3 | 361 | .003 | 0.33 (0.16,0.68) | .167, 44.1 | Fixed | 0.000 |
| Low dose | 7 | 520 | .007 | 0.60 (0.42,0.87) | .196, 30.4 | Fixed | |

CI = confidence interval, VAS = visual analog scale.

pregabalin and the VAS score with rest at 6, 12, and 24 hours. In addition, there was a positive correlation between the gabapentin dose and the VAS score at 12 hours. The dose–effect relationship between the dose of pregabalin and the VAS score with mobilization at 6, 12, and 24 hours was not determined because the included studies were limited, which may have biased the final results.

Pooled results indicated that pregabalin can decrease the VAS score with rest or mobilization at 6, 12, and 24 hours with clinical significance. Additionally, the dose–effect relationship between pregabalin and the VAS score at 6, 12, and 24 hours was determined. Results showed that the VAS score at 6, 12, and 24 hours had a tendency to decrease as the pregabalin dose increased. The difference was statistically significant ($P < .05$). These results were in accordance with a previous meta-analysis by Jiang et al,[36] in which the pain-relieving effects of pregabalin tended to increase as the dose of pregabalin increased in spinal surgery. However, another meta-analysis indicated that the pain control effects of pregabalin in total knee arthroplasty were limited and had no clinical importance.[37] The time of administration of pregabalin was 1 or 2 hours before anesthesia induction, and the dose of pregabalin ranged from 50 to 300 mg. Subgroup analysis results indicated that the high dose of pregabalin was superior to the low dose of pregabalin for pain management. An issue must be addressed that when the dose of pregabalin increased, the side effects of pregabalin were not reported. Thus, more studies are needed to determine the optimal dose of pregabalin in reducing acute pain in laparoscopic cholecystectomy patients.

The current meta-analysis indicated that the use of pregabalin can also decrease total morphine consumption in patients following laparoscopic cholecystectomy (WMD = −168.60, 95% CI −231.78, −105.42, $P = .000$). The reduction in the total dose of morphine was appropriately 168.60 mg. These morphine-reducing effects have obvious clinical importance. Dong et al[5] revealed that pregabalin can decrease the total morphine consumption at 48 hours by 2.23 mg in patients following total knee arthroplasty (MD = −2.23; 95% CI −2.48 to −1.97; $P < .001$).

Morphine-related complications were also compared between the pregabalin and control groups. A reduction in the incidence of postoperative nausea and vomiting following laparoscopic cholecystectomy was observed. To prevent a single case of nausea and vomiting, the NNT is 8.32 and 8.02, respectively. There were no significant differences in respiratory depression, pruritus, dizziness, blurred vision, and headache between the 2 groups ($P > .05$). Moreover, subgroup analyses results indicated that high-dose pregabalin can decrease the occurrence of nausea ($P < .05$).

There were several limitations in this meta-analysis as follows: the follow-up in the included studies ranged from 24 hours to 6 months, and the relatively short-term follow-up may underestimate the complication rate; the dosage and interval of pregabalin administration differed between the studies, and a subgroup analysis was conducted to decrease the heterogeneity, which could affect the precision of the results; multiple analgesic approaches differed from each other, and consistent multiple analgesic approaches are needed to identify the most effective pain control method; and publication bias existed in the VAS score at 12 hours and may affect the final results.

## 5. Conclusion

In conclusion, pregabalin was efficacious in the reduction of postoperative pain, total morphine consumption and morphine-related complications following laparoscopic cholecystectomy. In addition, a high dose of pregabalin was more effective than a low dose. The dose of pregabalin differed across the studies, and the heterogeneity was large. More high quality studies are needed to verify the optimal dose of pregabalin in laparoscopic cholecystectomy patients.

## References


[1] Wilson RG, Macintyre IM. Symptomatic outcome after laparoscopic cholecystectomy. Br J Surg 1993;80:439–41.
[2] Widdison AL. A systematic review of the effectiveness and safety of laparoscopic cholecystectomy. Ann R Coll Surg Engl 1996;78:476.
[3] Apfelbaum JL, Chen C, Mehta SS, et al. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg 2003;97:534–40. table of contents.
[4] Ravindran D. Chronic postsurgical pain: prevention and management. J Pain Palliat Care Pharmacother 2014;28:51–3.
[5] Dong J, Li W, Wang Y. The effect of pregabalin on acute postoperative pain in patients undergoing total knee arthroplasty: a meta-analysis. Int J Surg 2016;34:148–60.
[6] Bisgaard T, Rosenberg J, Kehlet H. From acute to chronic pain after laparoscopic cholecystectomy: a prospective follow-up analysis. Scand J Gastroenterol 2005;40:1358–64.
[7] Radhakrishnan M, Bithal PK, Chaturvedi A. Effect of preemptive gabapentin on postoperative pain relief and morphine consumption following lumbar laminectomy and discectomy: a randomized, double-blinded, placebo-controlled study. J Neurosurg Anesthesiol 2005;17:125–8.
[8] Dolin SJ, Cashman JN. Tolerability of acute postoperative pain management: nausea, vomiting, sedation, pruritus, and urinary retention. Evidence from published data. Br J Anaesth 2005;95:584–91.
[9] Pavlin DJ, Chen C, Penaloza DA, et al. Pain as a factor complicating recovery and discharge after ambulatory surgery. Anesth Analg 2002;95:627–34. table of contents.
[10] Sun XL, Zhao ZH, Ma JX, et al. Continuous local infiltration analgesia for pain control after yotal knee arthroplasty: a meta-analysis of randomized controlled trials. Medicine (Baltimore) 2015;94:e2005.
[11] Shahid M, Subhan F, Ahmad N, et al. Topical gabapentin gel alleviates allodynia and hyperalgesia in the chronic sciatic nerve constriction injury neuropathic pain model. Eur J Pain 2016;21:668–80.
[12] Park IJ, Kim G, Ko G, et al. Does preoperative administration of gabapentin/pregabalin improve postoperative nasal surgery pain? Laryngoscope 2016;126:2232–41.
[13] Yu L, Ran B, Li M, et al. Gabapentin and pregabalin in the management of postoperative pain after lumbar spinal surgery: a systematic review and meta-analysis. Spine (Phila Pa 1976) 2013;38:1947–52.
[14] Clarke H, Page GM, McCartney CJ, et al. Pregabalin reduces postoperative opioid consumption and pain for 1 week after hospital discharge, but does not affect function at 6 weeks or 3 months after total hip arthroplasty. Br J Anaesth 2015;115:903–11.
[15] Matthews EA, Dickenson AH. A combination of gabapentin and morphine mediates enhanced inhibitory effects on dorsal horn neuronal responses in a rat model of neuropathy. Anesthesiology 2002;96:633–40.
[16] Peng PW, Li C, Farcas E, et al. Use of low-dose pregabalin in patients undergoing laparoscopic cholecystectomy. Br J Anaesth 2010;105:155–61.
[17] Jokela R, Ahonen J, Tallgren M, et al. Premedication with pregabalin 75 or 150 mg with ibuprofen to control pain after day-case gynaecological laparoscopic surgery. Br J Anaesth 2008;100:834–40.
[18] Lam DM, Choi SW, Wong SS, et al. Efficacy of pregabalin in acute postoperative pain under different surgical categories: a meta-analysis. Medicine (Baltimore) 2015;94:e1944.
[19] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.
[20] Landis JR, Koch GG. An application of hierarchical kappa-type statistics in the assessment of majority agreement among multiple observers. Biometrics 1977;33:363–74.
[21] Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–74.
[22] Wang C, Cai X-Z, Yan S-G. Comparison of periarticular multimodal drug injection and femoral nerve block for postoperative pain management in total knee arthroplasty: a systematic review and meta-analysis. J Arthroplasty 2015;30:1281–6.

[23] GS HJ. Cochrane handbook for systematic reviews of interventions version 5.1.0. Available at: [http://handbook.cochrane.org/]. Accessed 2011.
[24] Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. N Engl J Med 1988;318:1728–33.
[25] Agarwal A, Gautam S, Gupta D, et al. Evaluation of a single preoperative dose of pregabalin for attenuation of postoperative pain after laparoscopic cholecystectomy. Br J Anaesth 2008;101:700–4.
[26] Balaban F, Yagar S, Ozgok A, et al. A randomized, placebo-controlled study of pregabalin for postoperative pain intensity after laparoscopic cholecystectomy. J Clin Anesth 2012;24:175–8.
[27] Bekawi MS, El Wakeel LM, Al Taher WM, et al. Clinical study evaluating pregabalin efficacy and tolerability for pain management in patients undergoing laparoscopic cholecystectomy. Clin J Pain 2014; 30:944–52.
[28] Chang SH, Lee HW, Kim HK, et al. An evaluation of perioperative pregabalin for prevention and attenuation of postoperative shoulder pain after laparoscopic cholecystectomy. Anesth Analg 2009;109:1284–6.
[29] Esmat IM, Farag HM. Comparative study between paracetamol and two different doses of pregabalin on postoperative pain in laparoscopic cholecystectomy. Saudi J Anaesth 2015;9:376–80.
[30] Gupta K, Sharma D, Gupta PK. Oral premedication with pregabalin or clonidine for hemodynamic stability during laryngoscopy and laparoscopic cholecystectomy: a comparative evaluation. Saudi J Anaesth 2011;5:179–84.
[31] Gurunathan U, Rapchuk IL, King G, et al. The effect of pregabalin and celecoxib on the analgesic requirements after laparoscopic cholecystectomy: a randomized controlled trial. J Anesth 2016;30: 64–71.
[32] Mishra R, Tripathi M, Chandola HC. Comparative clinical study of gabapentin and pregabalin for postoperative analgesia in laparoscopic cholecystectomy. Anesth Essays Res 2016;10:201–6.
[33] Parveen S, Negi DS, Kumar R, et al. Oral clonidine vs oral pregabalin premedication to attenuate pressor response to direct laryngoscopy in patients undergoing laparoscopic cholecystectomy: a randomized double blind study. J Clin Diagn Res 2016;10:Uc21–uc25.
[34] Sarakatsianou C, Theodorou E, Georgopoulou S, et al. Effect of preemptive pregabalin on pain intensity and postoperative morphine consumption after laparoscopic cholecystectomy. Surg Endosc 2013; 27:2504–11.
[35] Pandey CK, Navkar DV, Giri PJ, et al. Evaluation of the optimal preemptive dose of gabapentin for postoperative pain relief after lumbar diskectomy: a randomized, double-blind, placebo-controlled study. J Neurosurg Anesthesiol 2005;17:65–8.
[36] Jiang HL, Huang S, Song J, et al. Preoperative use of pregabalin for acute pain in spine surgery: a meta-analysis of randomized controlled trials. Medicine (Baltimore) 2017;96:e6129.
[37] Zhai L, Song Z, Liu K. The effect of gabapentin on acute postoperative pain in patients undergoing total knee arthroplasty: a meta-analysis. Medicine (Baltimore) 2016;95:e3673.