Systematic Review and Meta-Analysis

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Pregabalin can decrease acute pain and postoperative nausea and vomiting in hysterectomy

A meta-analysis

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Abstract

Background: Whether the preoperative administration of pregabalin plays a beneficial role in controlling acute pain after hysterectomy is unknown. We performed a systematic review and meta-analysis of randomized controlled trials (RCTs) to determine the efficacy and safety of the preoperative use of pregabalin to treat acute postoperative pain following hysterectomy.

Methods: In April 2017, a systematic computer-based search was conducted in the PubMed, EMBASE, Web of Science, Cochrane Library, and Google databases. RCTs comparing pregabalin with placebo in patients undergoing hysterectomy were retrieved. The primary endpoint was the visual analog scale (VAS) score with rest or mobilization at 2 h, 4 and 24 hours and cumulative morphine consumption at 2, 4, 24, and 48 hours. The secondary outcomes were complications of nausea, vomiting, sedation, and dizziness. After tests for publication bias and heterogeneity among studies were performed, the data were aggregated for random-effects models when necessary.

Results: Ten clinical studies with 1207 patients (pregabalin = 760, control = 447) were finally included in this meta-analysis. Preoperative administration of pregabalin was associated with a significant reduction of VAS with rest or mobilization at 2, 4, and 24 hours after hysterectomy. Further, the preoperative administration of pregabalin was associated with a reduction in total morphine consumption at 2, 4, 24, and 48 hours after hysterectomy. The occurrence of morphine-related complications (nausea and vomiting) was also reduced in the pregabalin group. However, the preoperative administration of pregabalin was associated with an increase in the occurrence of dizziness. There was no significant difference in the occurrence of sedation.

Conclusions: The preoperative use of pregabalin reduced postoperative pain, total morphine consumption, and morphine-related complications following hysterectomy. The doses of pregabalin were different, and large heterogeneity was the limitation of the current meta-analysis. Further studies should determine the optimal dose for controlling acute pain after hysterectomy.

Abbreviations: CI = confidence interval, NNH = number need 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, RR = risk ratio, SD = standard deviation, TKA = total knee arthroplasty, VAS = visual analog scale, WMD = weighted mean differences.

Keywords: acute pain, hysterectomy, meta-analysis, pregabalin

1. Introduction

High-quality pain control after hysterectomy remains a major challenge.[1] Appropriate pain control is a prerequisite to promoting early mobilization and functional recovery after hysterectomy.[2,3] Although opioid and nonsteroidal antiinflammatory medications are widely used for acute postoperative pain, some patients are bothered by drowsiness, nausea, and vomiting.[4] A multimodal anesthesia approach has been used for postoperative pain management. Central and peripheral sensitization was the cause of the pain. Thus, antihyperalgesic drugs may reduce postoperative pain and subsequent morphine-related complications by down-regulating central sensitization. Pregabalin is a structural analog of the inhibitory neurotransmitter γ-aminobutyric acid, but pregabalin is not functionally related with γ-aminobutyric acid.[5] Similar to its predecessor, gabapentin, it binds to the α-2-δ subunit of voltage-gated calcium channels, thereby reducing the release of several excitatory neurotransmitters and blocking the development of hyperalgesia and central sensitization.

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Although previous meta-analyses supported the use of pregabalin in reducing acute postoperative pain and limiting opioid use, particularly following total knee arthroplasty (TKA)[6,7] and spinal surgery,[8] to our knowledge, the role of pregabalin following hysterectomy has yet to be defined. The purpose of this meta-analysis was to study whether preoperative oral pregabalin administration was associated with lower pain scores and morphine consumption and fewer morphine-related complications.

2. Materials and methods

This meta-analysis was conducted in compliance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[9] and was written following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist.[10]

2.1. Search strategies

The following databases were searched in April 2017 without language restriction: PubMed (1950, April 2017), EMBASE (1974, April 2017), Web of Science (1950, April 2017), Cochrane Library (April 2017 Issue 3), and Google database (1974, April 2017). The MeSH terms and their combinations used in the search were as follows: "analgesia" OR "pain management" OR "anesthetic agents" OR "hysterectomy" OR "trachelectomy" OR "hysterectomy, vaginal" AND "pregabalin" OR "pregabalin" [MeSH terms]. The reference lists of related reviews and original articles were searched for any relevant studies, including randomized controlled trials (RCTs) involving adult humans. When multiple reports describing the same sample were published, the most recent or complete report was used. Because this is a meta-analysis, no ethics committee or institutional review board approval was necessary for the study.

2.2. Inclusion criteria and study selection

Patients: adults (age > 18 years) undergoing hysterectomy (abdominal hysterectomy; posthysterectomy and vaginal hysterectomy); *Intervention*: perioperative pregabalin as an intervention group; *Comparison*: placebo; Outcomes: visual analog scale (VAS) with rest or mobilization at 2, 4, and 24 hours, total morphine consumption at 2, 4, 24, and 48 hours and complications (nausea, vomiting, sedation and dizziness); *Study design*: RCTs. We excluded patients undergoing laparoscopic hysterectomy because the pain intensity of this surgery was much lower than that of abdominal hysterectomy. Two independent reviewers screened the titles and abstracts of the identified studies after removing 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; the acceptable threshold value was set at 0.61.[11,12]

2.3. Data abstraction

A specific extraction was performed to collect the following data from the included trials: patients' general characteristics, country, sample size of the control group and intervention group, preoperative and postoperative doses, and the timing and frequency of pregabalin use. Outcomes such as VAS with rest or mobilization at 2, 4, and 24 hours, total morphine consumption at 2, 4, 24, and 48 hours and complications (nausea, vomiting, sedation, and dizziness) were abstracted and recorded on a form. Pain severity after hysterectomy was measured by a 110-point VAS (0 = no pain and 100 = extreme pain). When the numerical rating scale (NRS) or verbal rating scale (VRS) was given and we accordingly converted NRS and VRS to VAS for next calculation. Additionally, a 11-point VAS was converted to a 110-point VAS.[13] Data in other forms (median or range of values) were also transformed to the mean ± standard deviation (SD) according to the conversion table made by Cochrane Handbook guideline.[14] All data were extracted by 2 independent reviewers, and disagreements were resolved by discussion.

2.4. Quality assessment

The methodological quality of all included trials was independently assessed by 2 reviewers using the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0 (http://handbook.cochrane.org/). A total of 7 items (random sequence generation, allocation concealment, blinding to the participant and personnel, blinding to the outcome assessment, incomplete outcome, selective reporting, and other bias) were measured. Each of the items was measured as "low risk of bias," "unclear risk of bias," and "high risk of bias." The risk of bias summary and risk of bias graph were obtained using Review Manager 5.3.0 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

2.5. Outcome measures and statistical analysis

Continuous outcomes (VAS with rest or mobilization at 2, 4, and 24 hours, total morphine consumption at 2, 4, 24, and 48 hours) were expressed as the weighted mean differences (WMD) and respective 95% CI. Dichotomous outcomes (nausea, vomiting, sedation, and dizziness) were expressed as the risk ratio (RR) with 95% CI. Statistical significance was set at $P < .05$ to summarize the findings across the trials. The meta-analysis was calculated by Stata software, version 13.0 (Stata Corp., College Station, TX). Statistical heterogeneity was tested using the Chi-squared test and I^2 statistic. When there was no statistical evidence of heterogeneity ($I^2 < 50\%$, $P > .1$), a fixed-effects model was adopted; otherwise, a random-effect model was chosen. Publication bias was tested using funnel plots. Publication bias was assessed by funnel plot and quantitatively assessed by Begg test. Subgroup analysis was based on the dose of pregabalin (<300 mg/d was identified as low dose, and ≥300 mg/d was identified as high dose). We considered there to be no publication bias if the funnel plot was symmetrical and the *P*-value was >.05. In addition, we calculated the number needed to harm (NNH) and the number need to treat (NNT) to examine the risks compared to the benefits of pregabalin therapy as it regarded complications.[15] The relationship between gabapentin dosage and the VAS at 12 and 24 hours was explored using the SPSS software (SPSS, Inc., Chicago, IL). The correlation coefficient (*r*) was used to evaluate the relationship between the dosage of pregabalin and the VAS with rest at 2, 4, and 24 hours, VAS with mobilization at 2, 4, and 24 hours, total morphine consumption at 2, 4, 24, and 48 hours, the occurrence of nausea, vomiting, sedation, and dizziness.

3. Results

3.1. Search results

The flow diagram is presented in Fig. 1. In the initial search, a total of 582 papers were identified from the electronic databases

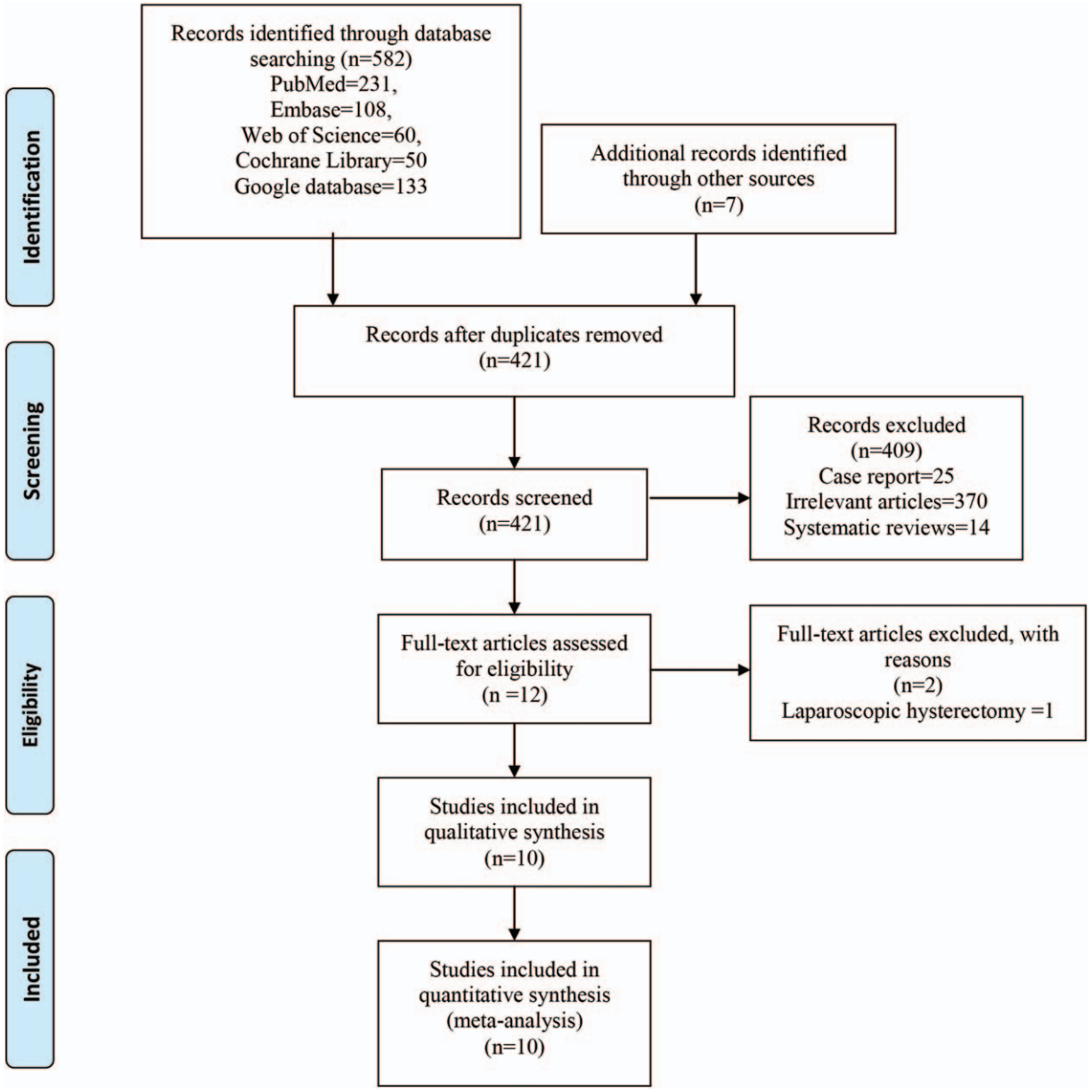

Figure 1. PRISMA flowchart for the included studies.

(PubMed = 231, EMBASE = 108, Web of Science = 60, Cochrane Library = 50, Google database = 133). Seven additional papers were identified through relevant references. Thus, a total of 589 papers were obtained in the initial search. These bibliographical references were introduced into the Endnote Software (Version X7, Thompson Reuters, Stanford, CA, USA), and duplicate papers were excluded. After removing duplicates, 421 papers were scanned, and 409 papers were excluded because they were irrelevant or did not meet the criteria. Then, the full-length papers were reviewed, and 2 studies[16,17] were excluded because they included laparoscopic hysterectomy. Four studies[18–21] administered different doses of pregabalin and thus were divided into 2 individual studies. One study used 3 different doses of pregabalin and was thus divided into 3 individual studies.[22] Ultimately, 10 clinical studies with 1207 patients (pregabalin = 760, control = 447) were included in the meta-analysis.[18–27]

The general characteristics of the included studies are presented in Table 1. The pregabalin dose ranged from 75 to 600 mg/d. The number of patients ranged from 20 to 167. Three types of hysterectomy were finally included (abdominal hysterectomy, posthysterectomy, and vaginal hysterectomy). The follow-up duration ranged from 24 hours to 6 months.

3.2. Quality assessment

The kappa value between the 2 reviewers was 0.825, which indicated that there was good agreement between the reviewers. The quality assessment of the included studies is summarized in Figs. 2 and 3. The risk of bias of random sequence generation showed an unclear risk of bias in 2 studies.[21,25] The risk of bias of allocation concealment showed an unclear risk of bias in 2 studies.[21,24] The risk of bias of blinding of participants and

Table 1

The general characteristic of the included studies.

Study	Country	Control group	Surgery	Intervention group			Outcomes	Follow-up	Total dose, mg/d
				No. of patients	Preoperative	Postoperative			
George et al[14]	Canada	Placebo (n=30)	Abdominal hysterectomy	Arm 1 (n=31)	Pregabalin 75 mg 2 h before surgery	12 h after initial dose	1,2,3,4,5,6,7, 8,9,10,11	6 mo	150
				Arm 2 (n=28)	Pregabalin 150 mg 2 h before surgery	12 h after initial dose			300
Mathiesen et al[26]	Denmark	Placebo (n=40)	Abdominal hysterectomy	39	Pregabalin 300 mg a day 1 h before anesthesia	No	1,2,3,9,10,11,12	48 h	300
Fassoulaki et al[23]	Greece	Placebo (n=40)	Abdominal hysterectomy	37	Pregabalin 150 mg 8 h before surgery	No	2,6,11,12,13	3 mo	150
Singla et al[19]	USA	Placebo (n=167)	Posthysterectomy	Arm 1=(161)	Pregabalin 150 mg 12 and 2 h before surgery	No	2,3,4,6,7,8, 9,10,11,12,13,14	1 y	150
				Arm 2=(166)	Pregabalin 300 mg 12 and 2 h before surgery	No			
Yucel et al[20]	Turkey	Placebo (n=30)	Abdominal hysterectomy	Arm 1 (n=30)	Pregabalin 150 mg 4 h before anesthesia induction	Pregabalin 150 mg 12 h after operation	5,6,9,10,12,13	48 h	300
				Arm 2 (n=30)	Pregabalin 300 mg 4 h before anesthesia induction	Pregabalin 300 mg 12 h after operation			600
Rajappa et al[21]	India	Placebo (n=30)	Vaginal hysterectomy	Arm 1 (n=45)	Pregabalin 75 mg 1 h before the patient was shifted to the operation theatre	No	2,3,9,10,11,12,13	48 h	75
				Arm 2 (n=45)	Pregabalin 150 mg 1 h before the patient was shifted to the operation theatre	No			150
Ittichaikulthol et al[25]	Thailand	Placebo (n=40)	Abdominal hysterectomy	38	Pregabalin 300 mg 1 h before surgery	No	2,3,9,10,11,12,13	48 h	300
Ghai et al[24]	India	Placebo (n=30)	Abdominal hysterectomy	30	Pregabalin 300 mg 1–2 h before surgery	No	2,3,9,10,11,12,13	24 h	300
Eman et al[27]	Turkey	Placebo (n=20)	Abdominal hysterectomy	20	Pregabalin 150 mg 1 h before surgery	No	2,3,9,10,11,12,13	1 mo	150
Przesmycki et al[22]	Polish	Placebo (n=20)	Abdominal hysterectomy	Arm 1 (n=20)	Pregabalin 75 mg 1 h before surgery	No	2,3,9,10,11,12,13	3 mo	75
				Arm 2 (n=20)	Pregabalin 150 mg 1 h before surgery	No	2,3,9,10,11,12,13		150
				Arm 3 (n=20)	Pregabalin300 mg 1 h before surgery	No	2,3,9,10,11,12,13	3 mo	300

h=hour.

1, VAS with rest at 2 h; 2, VAS with rest at 4 h; 3, VAS with rest at 24 h; 4, VAS with mobilization at 2 h; 5, VAS with mobilization at 4 h; 6, VAS with mobilization at 24 h; 7, total morphine consumption at 2 h; 8, total morphine consumption at 4 h; 9, total morphine consumption at 24 h; 10, total morphine consumption at 48 h; 11, the occurrence of nausea; 12, the occurrence of vomiting; 13, the occurrence of sedation; 14, the occurrence of dizziness.

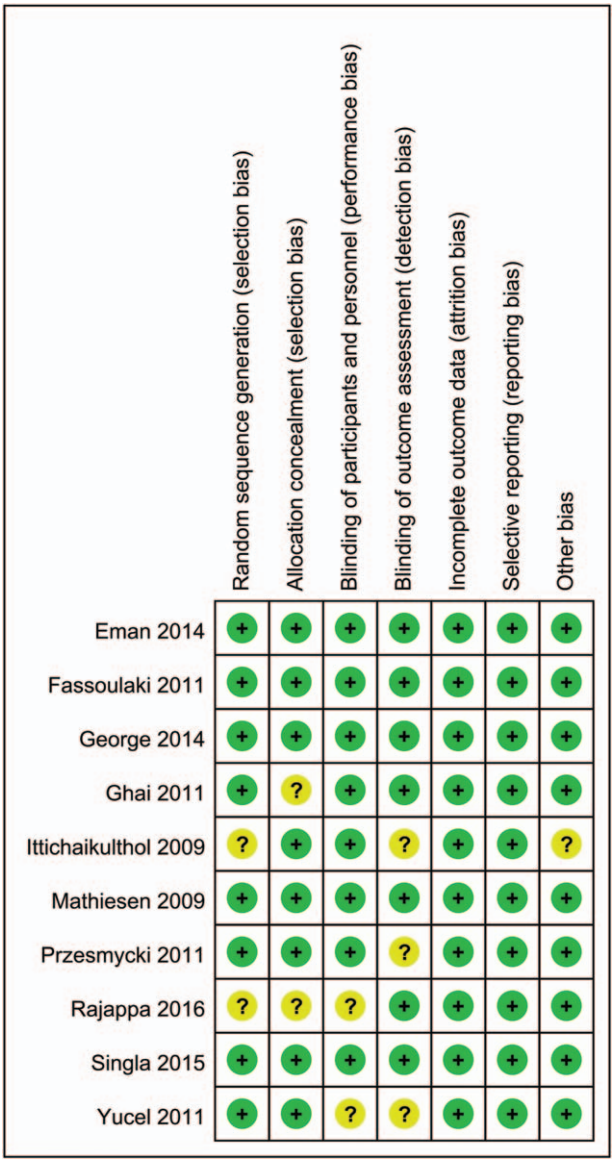

Figure 2. The risk of bias summary for the included studies.

personnel showed an unclear risk of bias in 2 studies.[20,21] The risk of bias of blinding of outcome assessment showed an unclear risk of bias in 3 studies.[20,22,25] The risk of bias of other bias showed an unclear risk of bias in one study because they did not state the sample calculation method.[25]

3.3. Results of meta-analysis

3.3.1. VAS with rest at 2, 4, and 24 hours. Pooled results indicated that preoperative administration of pregabalin was associated with reduced VAS at 2, 4, and 24 hours; this corresponded to a reduction of 11.39 points (WMD = −11.39, 95% CI: −15.60, −7.19, P = .000, Fig. 4) at 2 hours, 9.47 points (WMD = −9.47, 95% CI: −13.42, −5.52, P = .000, Fig. 5) at 4 hours, and 5.55 points at 24 hours (WMD = −5.55, 95% CI: −9.51, −1.58, P = .006, Fig. 6) on a 110-point VAS.

3.3.2. VAS with mobilization at 2, 4, and 24 hours. Pooled results indicated that preoperative administration of pregabalin was associated with reduced VAS at 2, 4, and 24 hours; this corresponded to a reduction of 11.39 points (WMD = −9.78, 95% CI: −14.14, −5.41, P = .000, Fig. 7) at 2 hours, 4.32 points (WMD = −4.32, 95% CI: −7.27, −1.36, P = .004, Fig. 8) at 4 hours, and 5.55 points at 24 hours (WMD = −2.88, 95% CI: −4.35, −1.42, P = .000, Fig. 9) on a 110-point VAS.

3.3.3. Total morphine consumption at 2, 4, 24, and 48 hours. Pooled results indicated that preoperative administration of pregabalin was associated with reduced total morphine consumption; this corresponded to a reduction of 2.08 mg (WMD = −2.08, 95% CI: −2.76, −1.39, P = .000, Fig. 10) at 2 hours, 5.36 mg (WMD = −5.36, 95% CI: −7.55, −3.18, P = .000, Fig. 11) at 4 hours, 10.94 mg (WMD = −10.94, 95% CI: −13.18, −8.71, P = .000, Fig. 12), and 19.29 mg at 24 hours (WMD = −19.29, 95% CI: −23.72, −14.86, P = .000, Fig. 13).

3.3.4. Complications. Pregabalin significantly reduced the occurrence of nausea by 9.91% (RR = 0.71, 95% CI: 0.53, 0.94, P = .016, NNT = 10.1, Fig. 14). Pregabalin also significantly reduced the occurrence of vomiting by 8.83% (RR = 0.67, 95% CI: 0.55, 0.83, P = .000, NNT = 11.3, Fig. 15).

There were no significant differences between the groups in the occurrence of sedation (RR = 0.93, 95% CI: 0.79, 1.08, P = .339, NNT = 118.4, Fig. 16). However, pregabalin increased the occurrence of dizziness by 16.7% (RR = 1.75, 95% CI: 1.06, 2.89, P = .028, NNH = 5.88, Fig. 17).

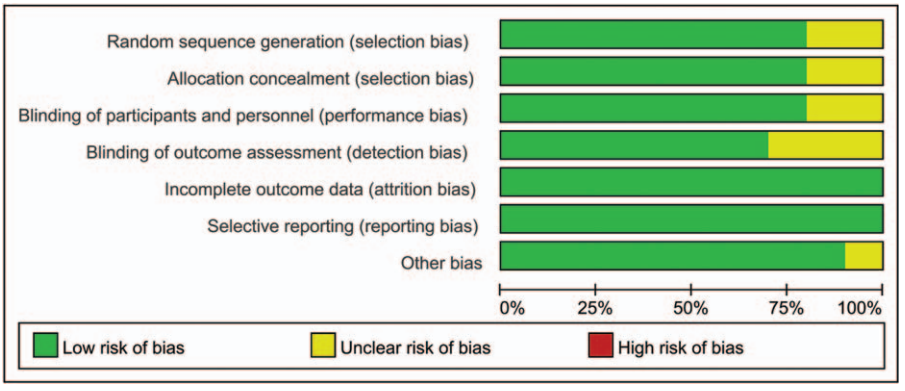

Figure 3. The risk of bias graph for the included studies.

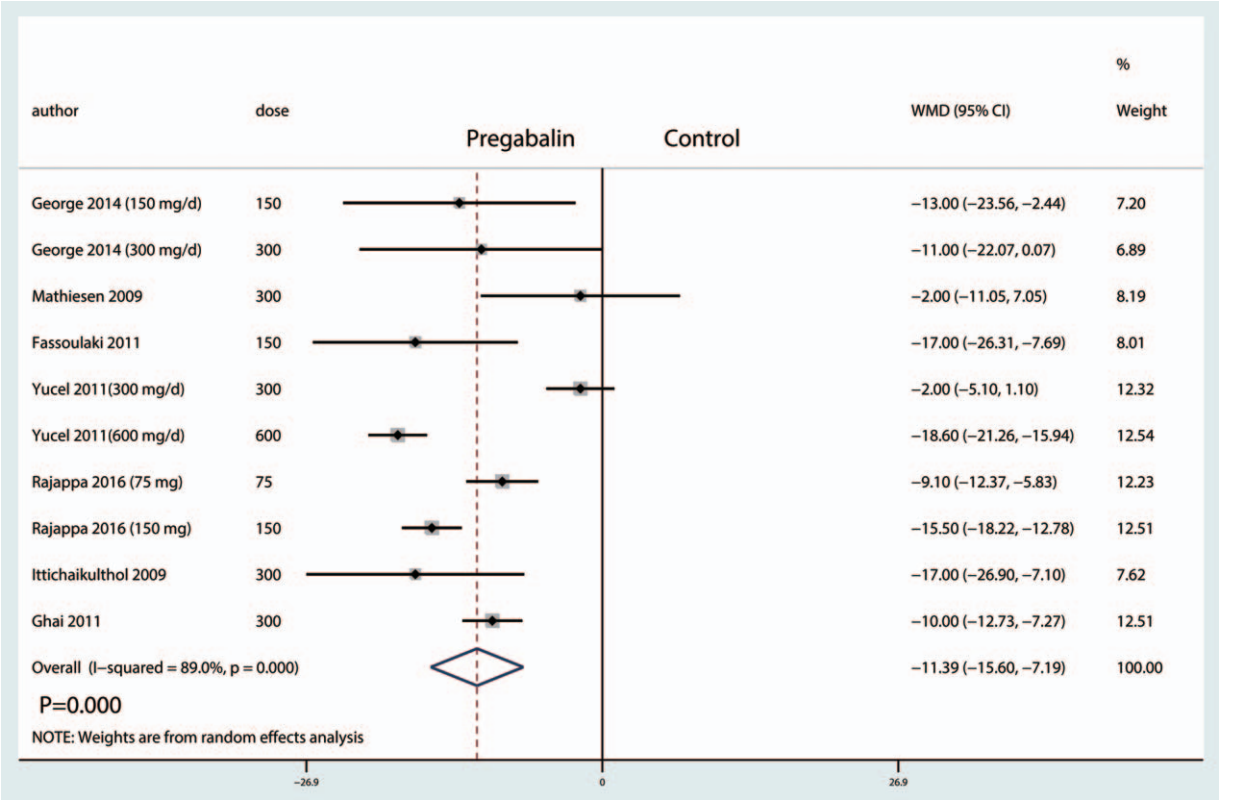

Figure 4. Forest plot comparing VAS with rest at 2 hours between the pregabalin group and the control group.

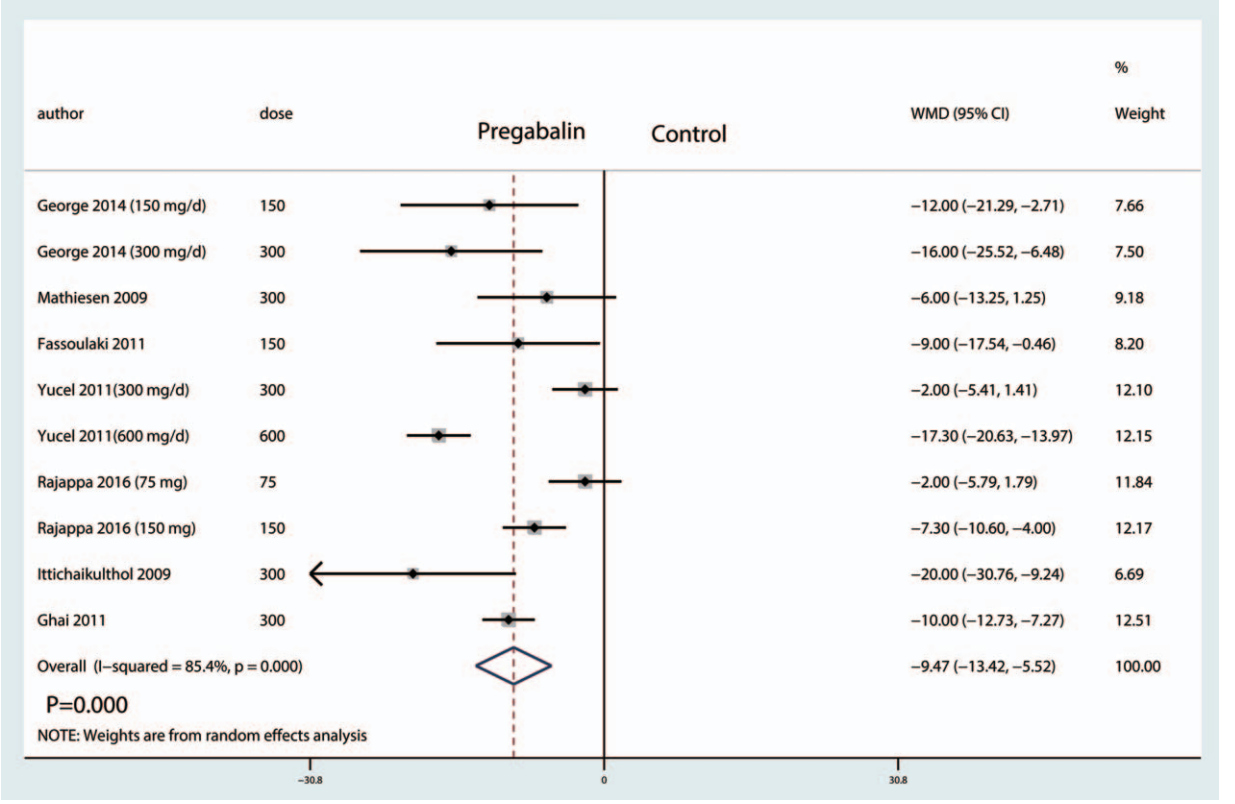

Figure 5. Forest plot comparing VAS with rest at 4 hours between the pregabalin group and the control group.

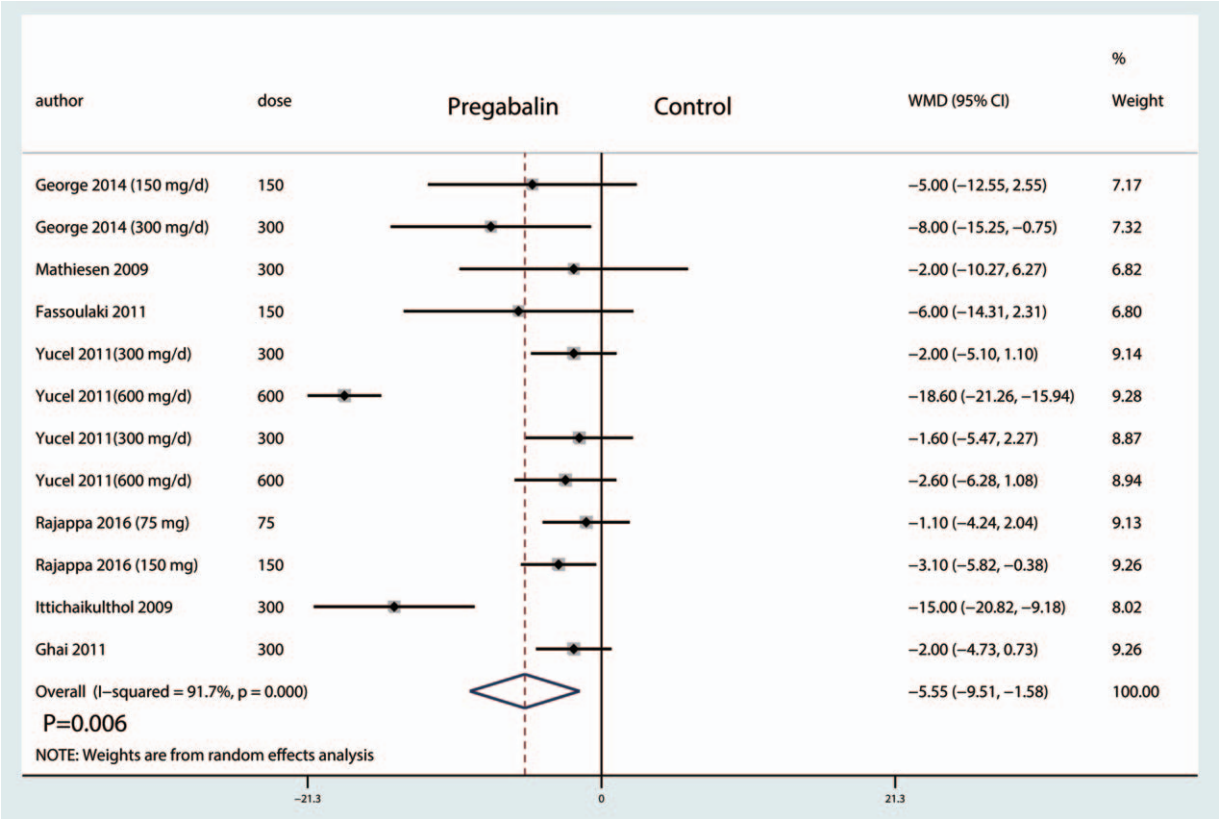

Figure 6. Forest plot comparing VAS with rest at 24 hours between the pregabalin group and the control group.

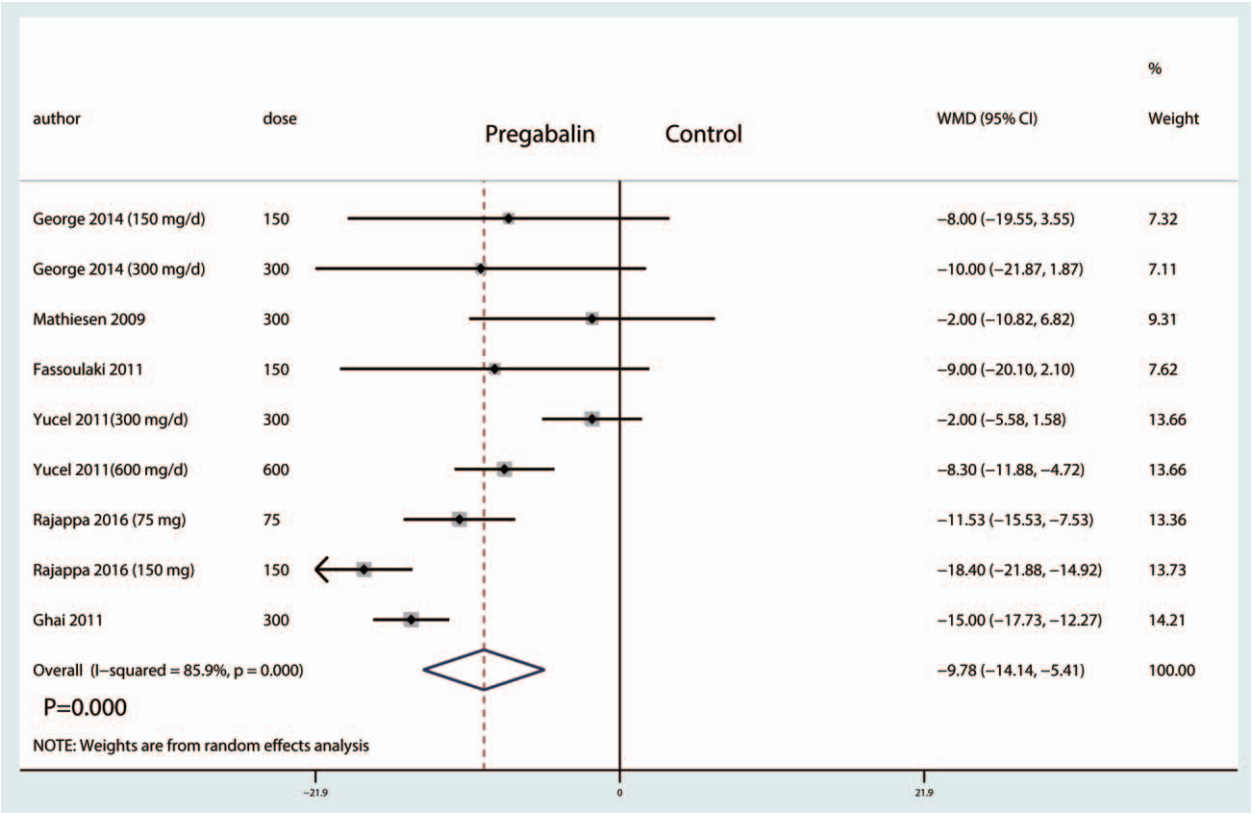

Figure 7. Forest plot comparing VAS with mobilization at 2 hours between the pregabalin group and the control group.

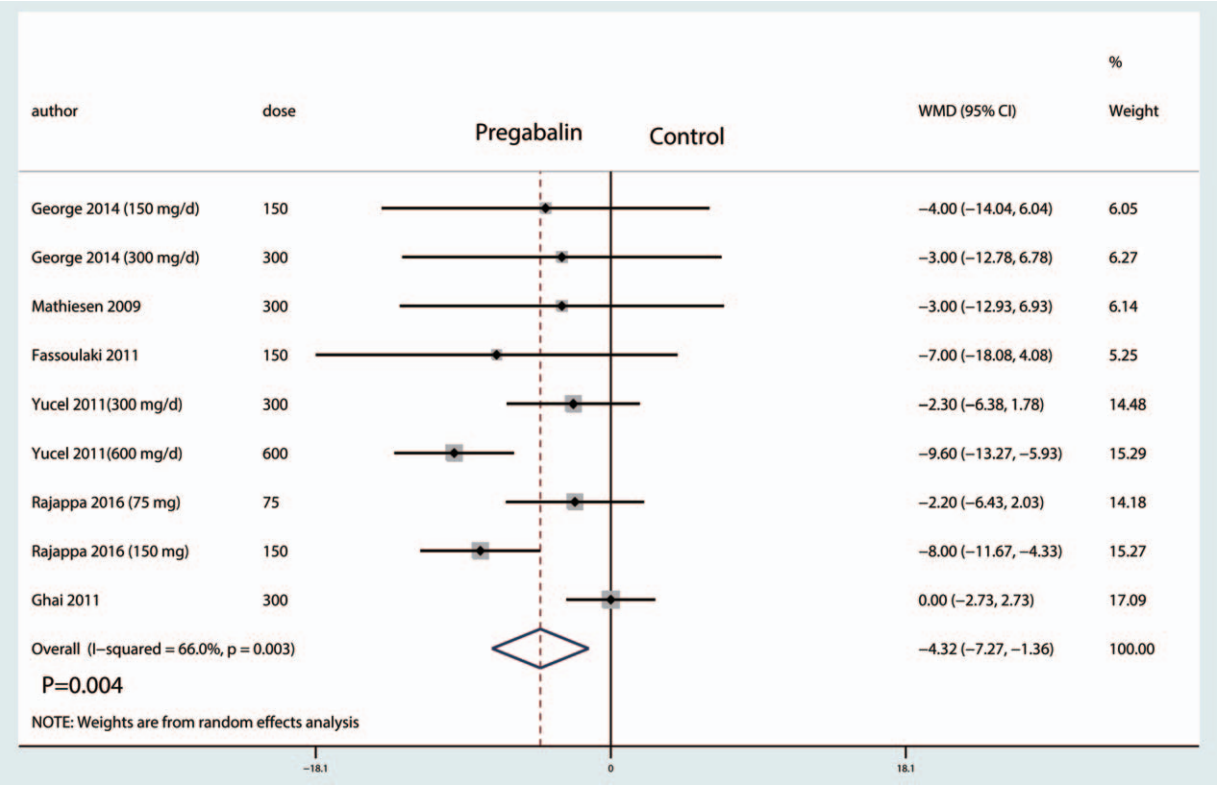

Figure 8. Forest plot comparing VAS with mobilization at 4 hours between the pregabalin group and the control group.

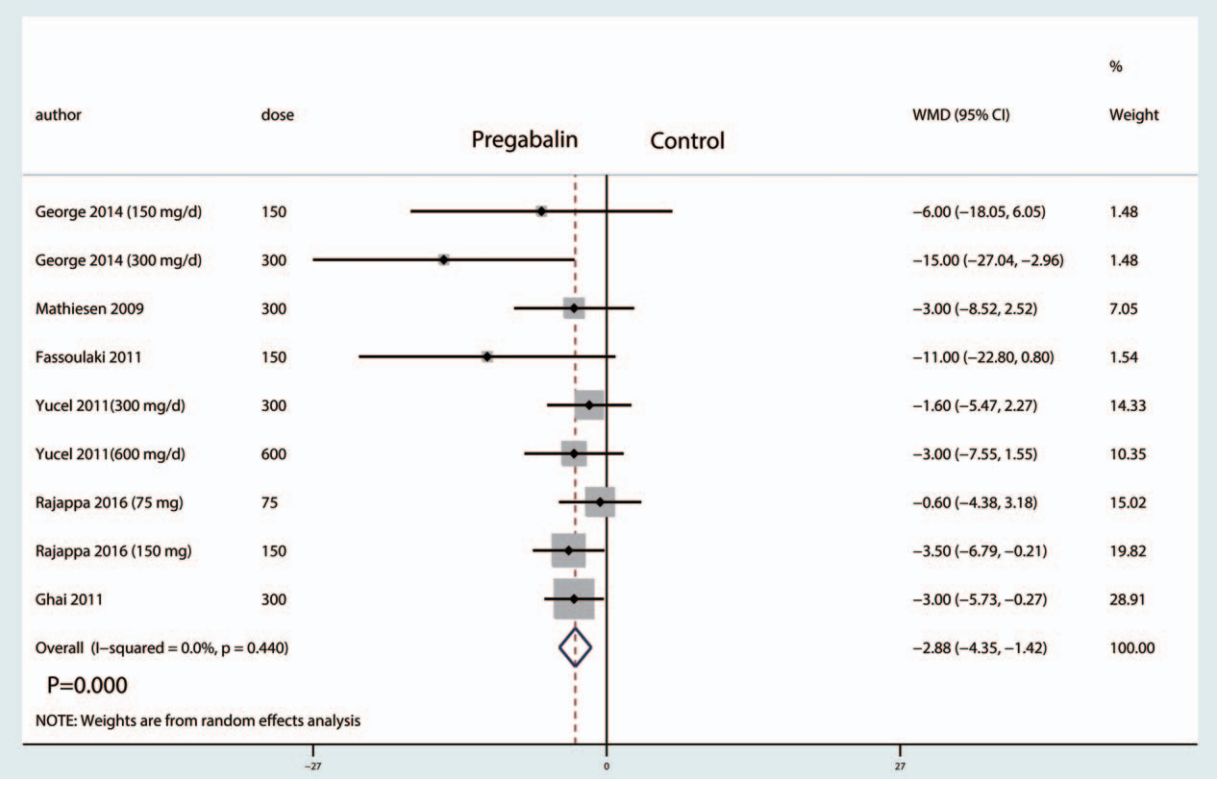

Figure 9. Forest plot comparing VAS with mobilization at 24 hours between the pregabalin group and the control group.

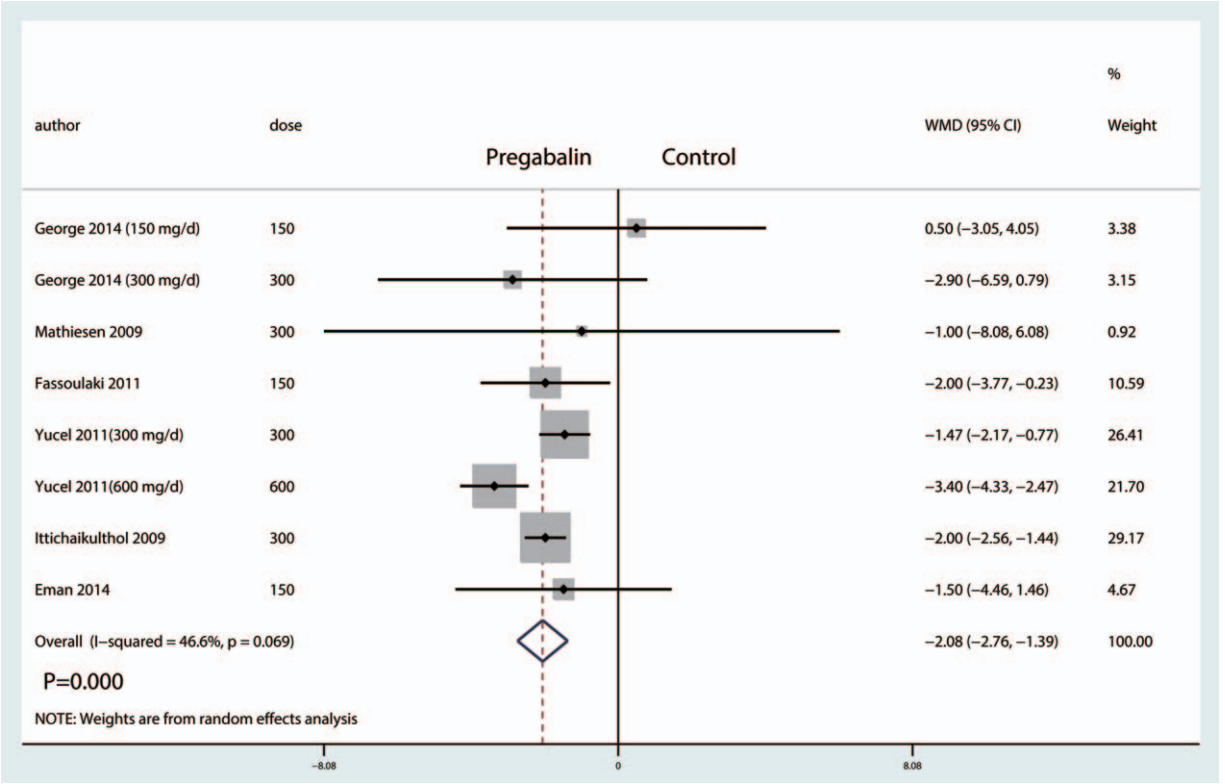

Figure 10. Forest plot comparing total morphine consumption at 2 hours between the pregabalin group and the control group.

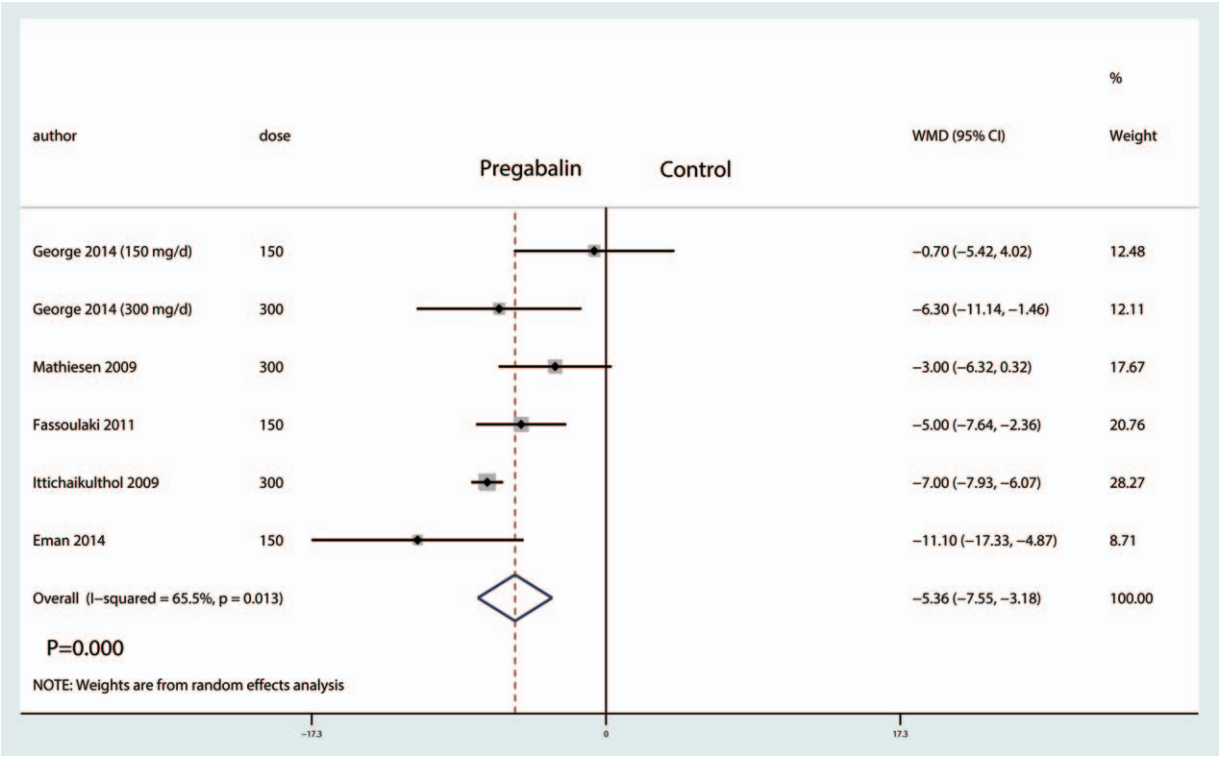

Figure 11. Forest plot comparing total morphine consumption at 4 hours between the pregabalin group and the control group.

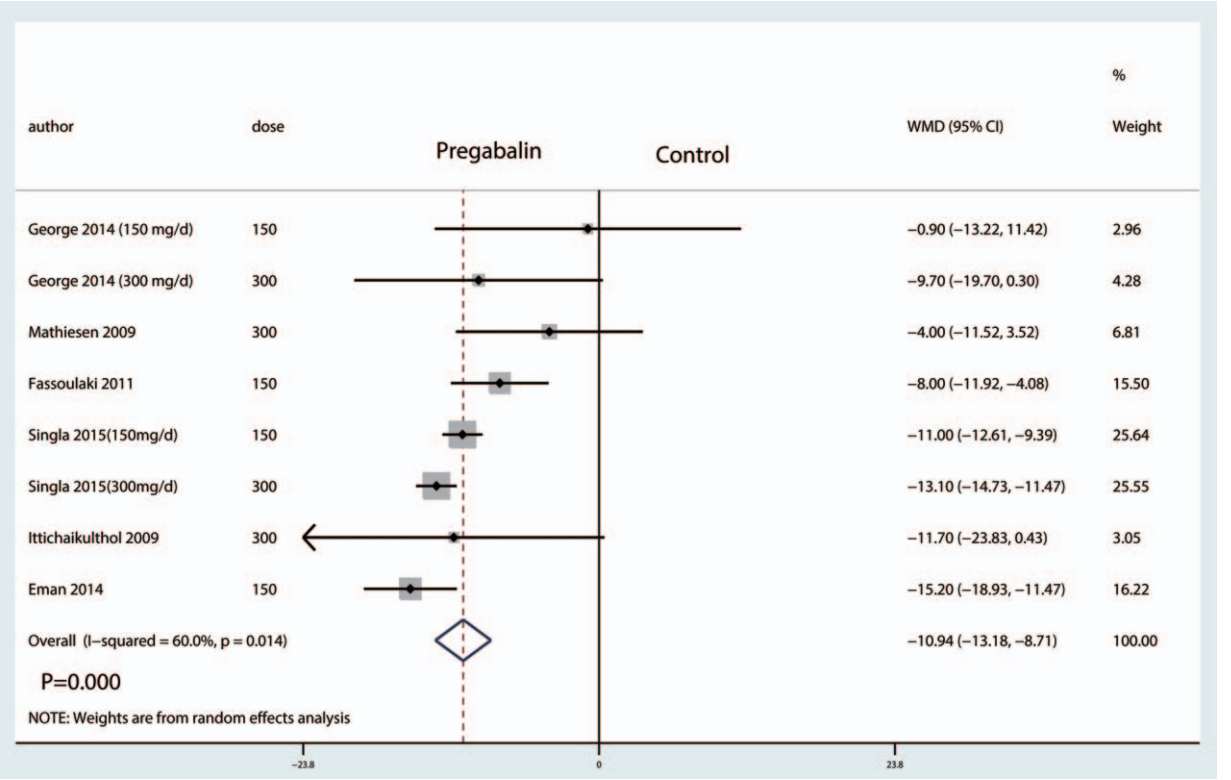

Figure 12. Forest plot comparing total morphine consumption at 24 hours between the pregabalin group and the control group.

3.3.5. Subgroup analysis. Subgroup analyses were conducted based on the dose of pregabalin; detailed results are shown in Table 2. The subgroup results indicated that high dose pregabalin was superior to low dose pregabalin in VAS with rest at 4 and 24 hours and total morphine consumption at 48 hours. Furthermore, high dose pregabalin was associated with an increase in the occurrence of dizziness (RR = 2.99, 2.17, 4.11).

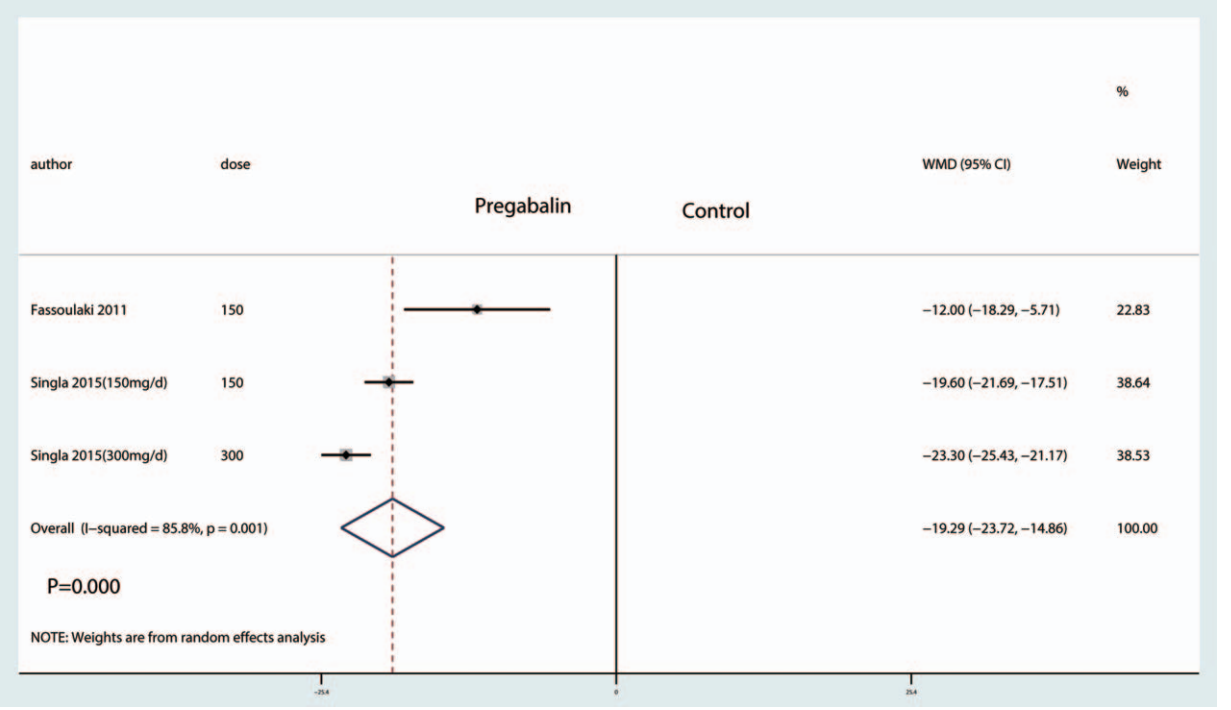

Figure 13. Forest plot comparing total morphine consumption at 48 hours between the pregabalin group and the control group.

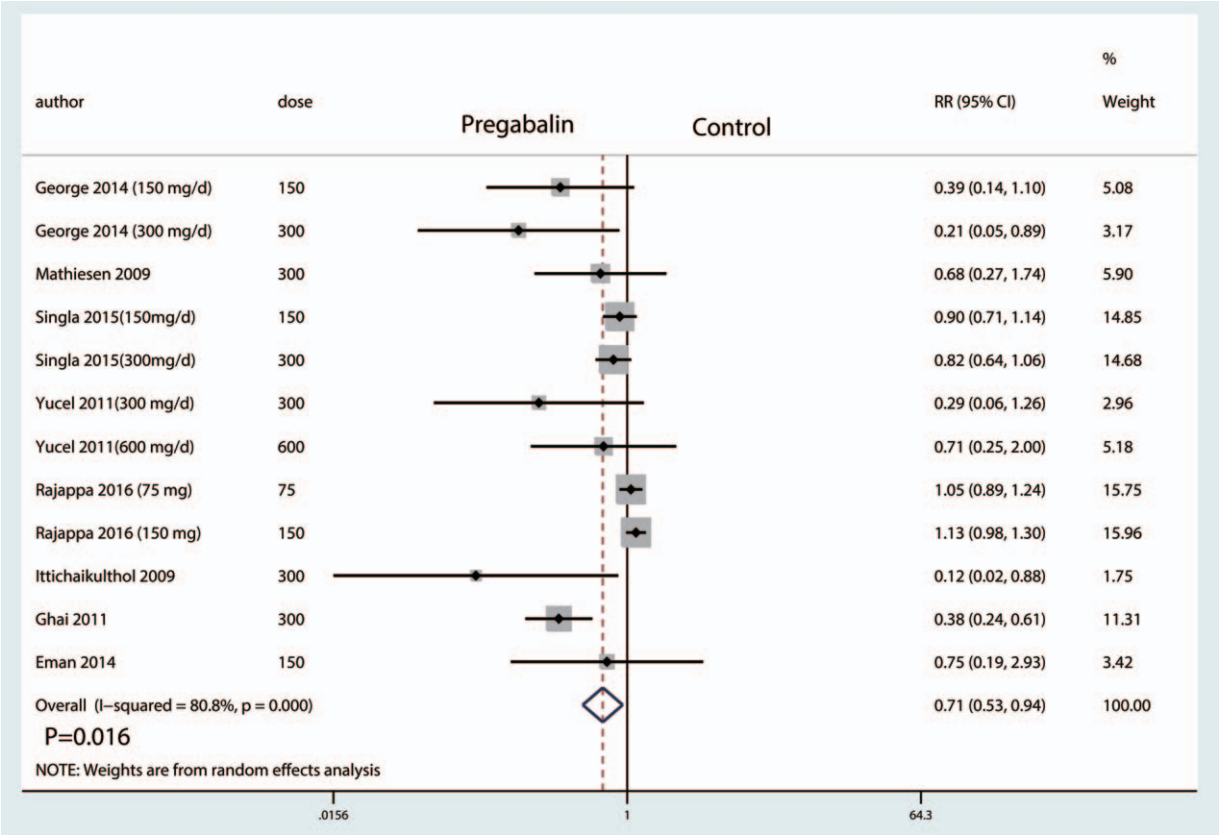

Figure 14. Forest plot comparing the occurrence of nausea between the pregabalin group and the control group.

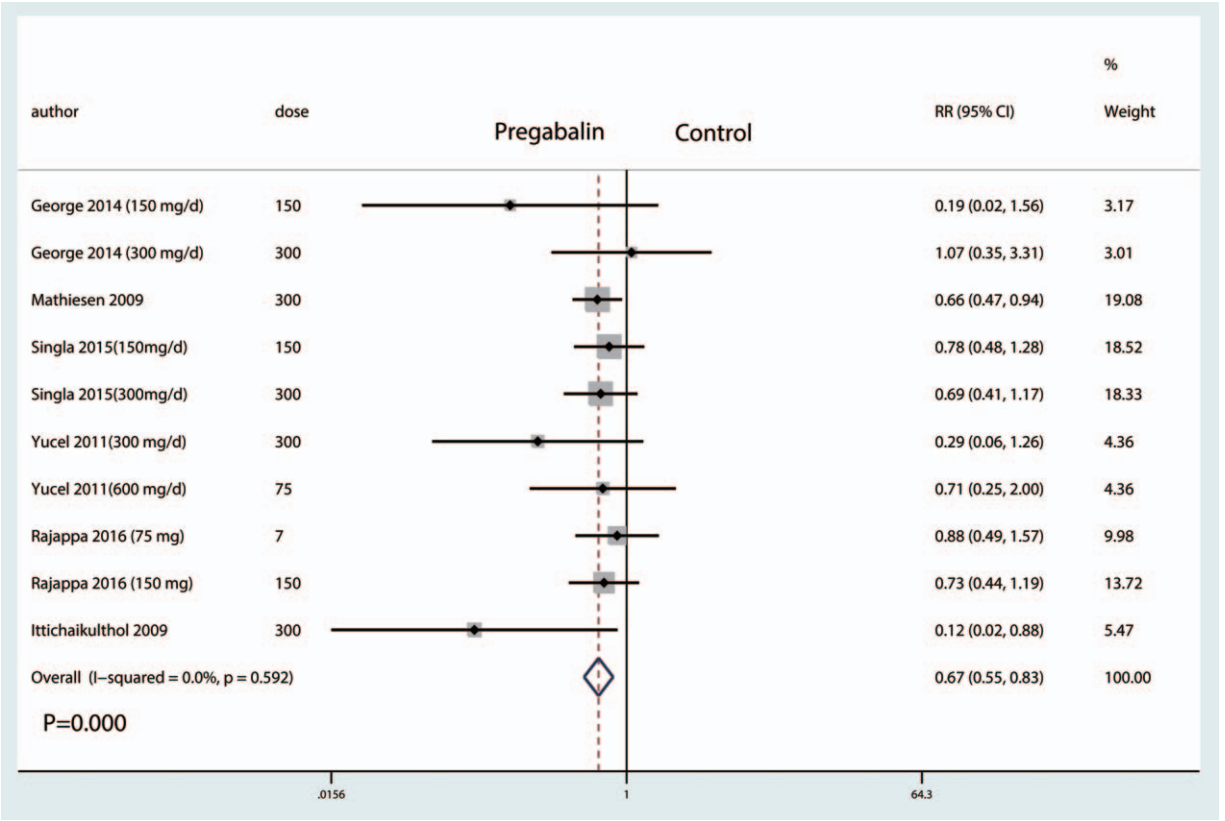

Figure 15. Forest plot comparing the occurrence of vomiting between the pregabalin group and the control group.

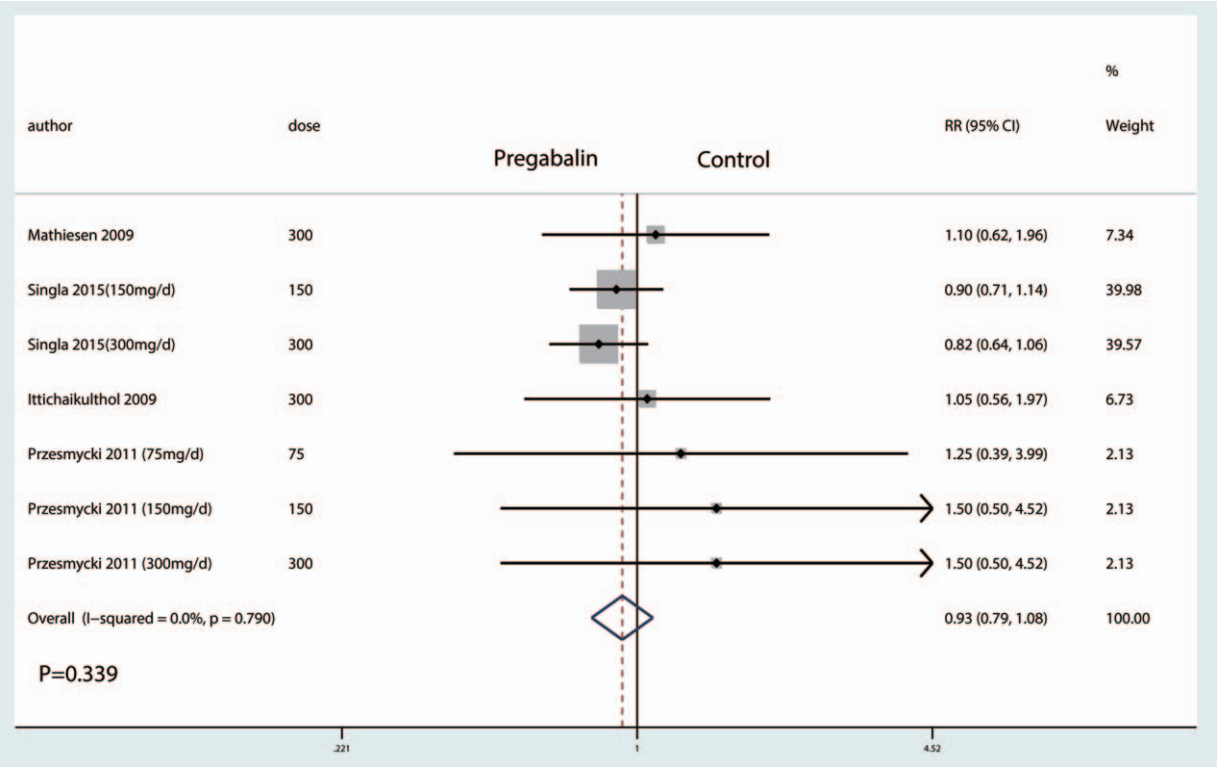

Figure 16. Forest plot comparing the occurrence of sedation between the pregabalin group and the control group.

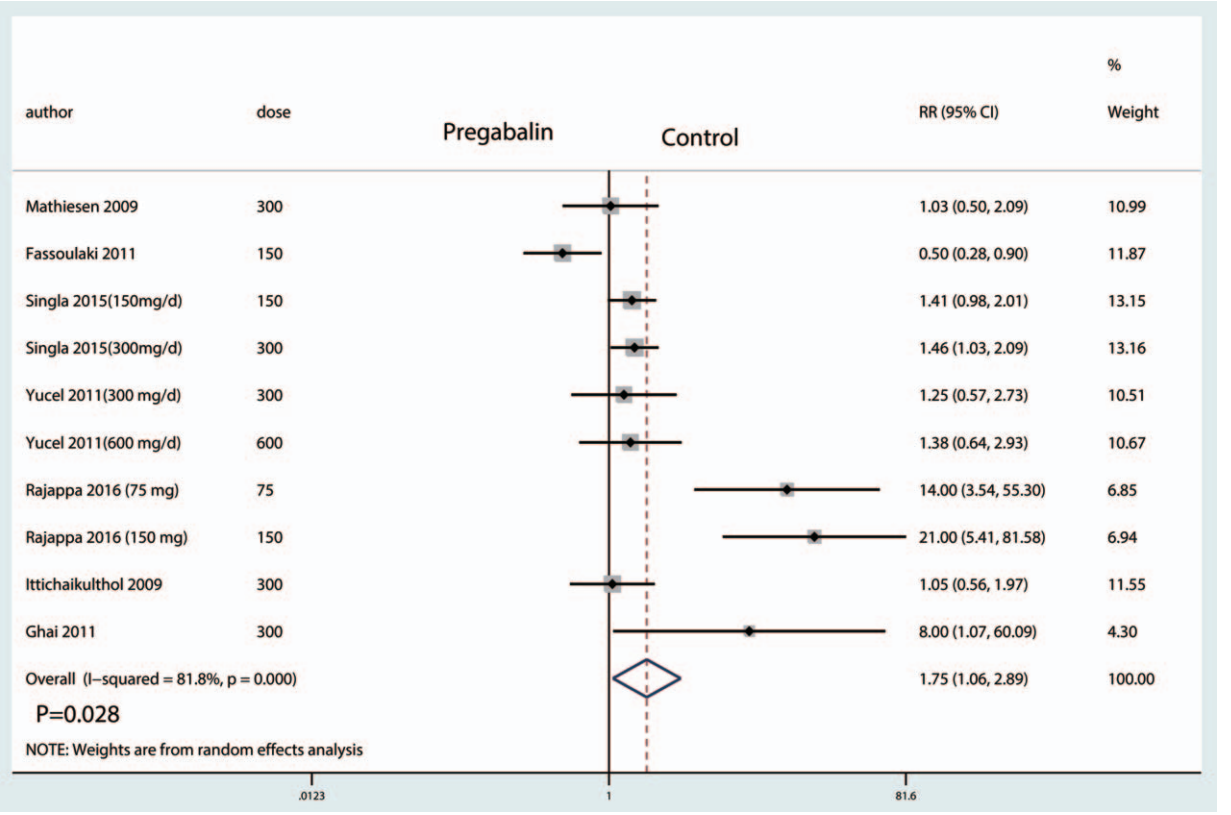

Figure 17. Forest plot comparing the occurrence of dizziness between the pregabalin group and the control group.

Table 2

Subgroup analysis of the outcomes according to the dose of pregabalin.

Variables	Studies (n)	Patients (n)	Incidence				
			P	Weighted mean difference (95% CI)	Heterogeneity *P* (I^2)	Model	Subgroup difference
VAS with rest at 2 h							
Low dose	4	326	.000	−13.16 (−17.62, −8.71)	.024, 68.2	Random	.116
High dose	6	160	.003	−10.06 (−16.75, −3.38)	.000, 92.8	Random	
VAS with rest at 4 h							
Low dose	4	351	.002	−6.40 (−10.47, −2.33)	.075, 58.5	Random	.023
High dose	6	180	.000	−11.25 (−17.05, −5.46)	.000, 89.0	Random	
VAS with rest at 24 h							
Low dose	4	351	.008	−2.63 (−4.56, −0.70)	.565, 0.0	Fixed	.036
High dose	8	180	.024	−6.49 (−12.13, −0.85)	.000, 94.0	Random	
VAS with mobilization at 2 h							
Low dose	4	406	.000	0.45 (0.24, 0.83)	.632, 0.0	Fixed	
High dose	7	360	.015	0.81 (0.40, 1.63)	.981, 0.0	Fixed	
VAS with mobilization at 4 h							
Low dose	4	370	.003	−7.62 (−13.76, −1.46)	.028, 66.9	Random	.181
High dose	5	406	.009	−3.67 (−8.16, −1.85)	.234, 76.7	Random	
VAS with mobilization at 24 h							
Low dose	4	326	.048	−2.89 (−5.75, −0.03)	.308, 16.7	Fixed	.337
High dose	5	160	.003	−2.99 (−4.88, −1.01)	.364, 7.4	Fixed	
Total morphine consumption at 2 h							
Low dose	3	160	.036	−1.50 (−2.90, −0.10)	.467, 0.0	Fixed	.032
High dose	5	120	.000	−2.24 (−3.08, −1.40)	.027, 63.5	Random	
Total morphine consumption at 4 h							
Low dose	3	160	.030	−5.20 (−9.89, −0.50)	.033, 70.8	Random	.208
High dose	3	120	.000	−5.68 (−8.35, −3.02)	.074, 61.5	Random	
Total morphine consumption at 24 h							
Low dose	4	156	.000	−10.69 (−14.16, −7.22)	.021, 69.0	Random	.109
High dose	4	200	.000	−10.34 (−15.07, −5.62)	.1251, 47.7	Random	
Total morphine consumption at 48 h							
Low dose	2		.000	−16.40 (−23.76, −9.05)	.025, 80.2	Random	.115
High dose	1		.000	−23.30 (−25.43, −21.17)	–	–	
The occurrence of nausea							
Low dose	4	160	.508	0.96 (0.84, 1.09)	.020, 69.6	Random	.001
High dose	7	120	.000	0.61 (0.50, 0.75)	.020, 60.0	Random	
The occurrence of vomiting							
Low dose	5	160	.042	0.74 (0.56, 0.99)	.745, 0.0	Fixed	.132
High dose	5	120	.001	0.61 (0.45, 0.81)	.285, 20.3	Fixed	
The occurrence of sedation							
Low dose	4	156	.396	0.91 (0.74, 1.13)	.564, 0.0	Fixed	.255
High dose	3	200	.630	0.94 (0.75, 1.19)	.588, 0.0	Fixed	
The occurrence of dizziness							
Low dose	7		.108	1.20 (0.96, 1.50)	.000, 93.3	Random	.000
High dose	3		.000	2.99 (2.17, 4.11)	.032, 56.5	Random	

CI = confidence interval, VAS = visual analog scale.

3.3.6. Sensitivity analysis, publication bias, and dose–effect relationship. Sensitivity analysis of the VAS with rest at 2, 4, and 24 hours and VAS with mobilization at 2, 4, and 24 hours is shown in Supplement S1, http://links.lww.com/MD/B821. The results indicated that none of the studies affected the final results. The publication bias of VAS with rest at 2, 4, and 24 hours and VAS with mobilization at 2, 4, and 24 hours were assessed by funnel plot and quantified by Begg test. The results indicated that there was no publication bias among the included studies (Supplement S2, http://links.lww.com/MD/B821).

Dose–effect relationship between the pregabalin dose and the VAS with rest at 2, 4, and 24 hours, VAS with mobilization at 2, 4, and 24 hours, total morphine consumption at 2, 4, 24, and 48 hours, the occurrence of nausea, vomiting, sedation, and dizziness are shown in Supplement S3, http://links.lww.com/MD/B821. There was a negative correlation among the pregabalin dose, the VAS with mobilization at 24 hours ($r = -0.860$, $P = .001$, Supplement S3-1F, http://links.lww.com/MD/B821) and the occurrence of nausea ($r = -0.434$, $P = .035$, Supplement S3-2E, http://links.lww.com/MD/B821).

4. Discussion

The current meta-analysis demonstrated that the use of pregabalin is associated with reduced pain scores at 2, 4, and 24 hours with rest or mobilization, which is equivalent on a 110-point VAS to 11.39 points at 2 hours, 9.47 points at 4 hours and 5.55 points at 24 hours with rest and 11.39 points at 2 hours, 4.32 points at 4 hours and 5.55 points at 24 hours. The cumulative morphine consumption at 2, 12, 24, and 48 hours was reduced in the pregabalin group by approximately 2.08, 5.36, 10.94, and 19.29 mg, respectively. The most important

finding of this meta-analysis was that pregabalin can reduce the occurrence of nausea and vomiting after hysterectomy. There was no significant difference in terms of sedation; however, pregabalin increased the occurrence of dizziness after hysterectomy.

A major strength of the current meta-analysis was that we comprehensively searched the electronic databases (PubMed, EMBASE, Web of Science, Cochrane Library, and Google database) and calculated the relevant outcomes in a statistically rigorous method. We included RCTs and excluded non-RCTs, and thus the selective risk of bias was largely eliminated. The quality ratings of the included RCTs were high or moderate. The only factor that reduced the level of evidence was the heterogeneity between the studies, which was caused by the different doses and time intervals of the pregabalin used. In the end, we performed a subgroup analysis according to the dose to reduce the heterogeneity.

These results are consistent with those of previous meta-analyses assessing the use of pregabalin in the management of acute postsurgical pain that have found that its use was associated with significant reductions in pain following tonsillectomy, knee surgery, hip surgery, nasal surgery, and spinal surgery.[6–8,28–30] However, Hamilton et al[31] found no evidence to support the routine use of gabapentinoids (gabapentin and pregabalin) in the management of acute pain following TKA. One possible reason was that they included both gabapentin and pregabalin to analyze the relevant results. The current meta-analysis indicated that preoperative administration pregabalin was effective in reducing acute pain and total morphine consumption. Mishriky et al[32] found that a single preoperative dose was as effective as multiple doses and that low doses (<75 mg) of pregabalin were as effective as high dose (300 mg) pregabalin in terms of reducing total morphine consumption. We calculated a dose–effect relationship between the pregabalin dose and the VAS score, total morphine consumption and the adverse complications. The results indicated that there was a negative correlation between the pregabalin dose and both the VAS with mobilization at 24 hours ($r=-0.860$, $P=.001$) and the occurrence of nausea ($r=-0.434$, $P=.035$).

A significant reduction in the incidence of postoperative nausea (NNT = 10.1) and vomiting (NNT = 11.3) following hysterectomy was associated with pregabalin. Thus, this antiemetic effect is likely to be due to reduced total morphine consumption and is likely to be via alternative mechanisms.[33] A major concern of pregabalin was that it may be associated with an increase in the occurrence of dizziness and sedation. Meta-analysis results indicated that there was no significant difference in the occurrence of sedation (RR = 0.93, 95% CI: 0.79, 1.08, $P=.339$). Lam et al[34] found that the incidence of adverse effects of pregabalin was not equal in different surgical categories.

Future research should be focused on the timing, dose and interval of pregabalin to maximize the analgesic efficacy without increasing the occurrence of dizziness. Furthermore, long-term follow-up should be included to determine whether pretreatment with pregabalin has a beneficial role on patient satisfaction.

There were several limitations to this meta-analysis: only 10 RCTs were included, and the sample sizes of the included studies were relatively small, which might have affected the precision of the effect size estimation; the follow-up durations of the included studies were different, and the satisfaction of the patients was not assessed; the dosage and timing of pregabalin administration differed between the studies, although a subgroup analysis was conducted to decrease the heterogeneity, which would affect the precision of the results; the multiple analgesia approaches differed among studies, and consistent analgesia approaches are needed to identify the most effective pain control method; and different types of hysterectomy (abdominal hysterectomy; posthysterectomy and vaginal hysterectomy) were included and will affect the final results.

5. Conclusion

In conclusion, this is the first meta-analysis to compare the preoperative use of pregabalin versus a placebo in managing pain after hysterectomy. Some analgesic efficacy and opioid-sparing effects were observed with the administration of pregabalin. Additionally, a significant decrease in the risk of nausea and vomiting was associated with the use of pregabalin. Because the sample size and the number of included studies were limited, a multicenter RCT is needed to identify the effects of pregabalin for reducing acute pain after hysterectomy.

References

[1] Hayden JM, Oras J, Karlsson OI, et al. Post-operative pain relief using local infiltration analgesia during open abdominal hysterectomy: a randomized, double-blind study. Acta Anaesthesiol Scand 2017;61: 539–48.

[2] Steinberg AC, Schimpf MO, White AB, et al. Preemptive analgesia for postoperative hysterectomy pain control: systematic review and clinical practice guidelines. Am J Obstet Gynecol 2017;[Epub ahead of print].

[3] Kim NS, Lee JS, Park SY, et al. Oxycodone versus fentanyl for intravenous patient-controlled analgesia after laparoscopic supracervical hysterectomy: a prospective, randomized, double-blind study. Medicine (Baltimore) 2017;96:e6286.

[4] Jarahzadeh MH, Harati ST, Babaeizadeh H, et al. The effect of intravenous magnesium sulfate infusion on reduction of pain after abdominal hysterectomy under general anesthesia: a double-blind, randomized clinical trial. Electron Physician 2016;8:2602–6.

[5] Ben-Menachem E. Pregabalin pharmacology and its relevance to clinical practice. Epilepsia 2004;45(suppl 6):13–8.

[6] 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.

[7] Li F, Ma J, Kuang M, et al. The efficacy of pregabalin for the management of postoperative pain in primary total knee and hip arthroplasty: a meta-analysis. J Orthop Surg Res 2017;12:49.

[8] 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.

[9] Higgins JPT, G. S. Cochrane handbook for systematic reviews of interventions version 5.1.0. 2011; Available at: http://www.cochrane-handbook.org. Accessed 2011

[10] 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.

[11] 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.

[12] Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–74.

[13] 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.

[14] GS, H. J. Cochrane handbook for systematic reviews of interventions version 5.1.0[updated March 2011]. 2011.

[15] 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.

[16] Jokela R, Ahonen J, Tallgren M, et al. A randomized controlled trial of perioperative administration of pregabalin for pain after laparoscopic hysterectomy. Pain 2008;134:106–12.

[17] Asgari Z, Rouholamin S, Nataj M, et al. Dose ranging effects of pregabalin on pain in patients undergoing laparoscopic hysterectomy: a randomized, double blinded, placebo controlled, clinical trial. J Clin Anesth 2017;38:13–7.
[18] George RB, McKeen DM, Andreou P, et al. A randomized placebo-controlled trial of two doses of pregabalin for postoperative analgesia in patients undergoing abdominal hysterectomy. Can J Anaesth 2014;61: 551–7.
[19] Singla NK, Chelly JE, Lionberger DR, et al. Pregabalin for the treatment of postoperative pain: results from three controlled trials using different surgical models. J Pain Res 2015;8:9–20.
[20] Yucel A, Ozturk E, Aydogan MS, et al. Effects of 2 different doses of pregabalin on morphine consumption and pain after abdominal hysterectomy: a randomized, double-blind clinical trial. Curr Ther Res Clin Exp 2011;72:173–83.
[21] Rajappa GC, Vig S, Bevanaguddaiah Y, et al. Efficacy of pregabalin as premedication for post-operative analgesia in vaginal hysterectomy. Anesth Pain Med 2016;6:e34591.
[22] Przesmycki K, Wiater-Koziol E, Kotarski J, et al. Effect of pre-emptive pregabalin on pain intensity and morphine requirement after hysterectomy. Anestezjol Intens Ter 2011;43:14–7.
[23] Fassoulaki A, Melemeni A, Tsaroucha A, et al. Perioperative pregabalin for acute and chronic pain after abdominal hysterectomy or myomectomy: a randomised controlled trial. Eur J Anaesthesiol 2012;29:531–6.
[24] Ghai A, Gupta M, Hooda S, et al. A randomized controlled trial to compare pregabalin with gabapentin for postoperative pain in abdominal hysterectomy. Saudi J Anaesth 2011;5:252–7.
[25] Ittichaikulthol W, Virankabutra T, Kunopart M, et al. Effects of pregabalin on post operative morphine consumption and pain after abdominal hysterectomy with/without salphingo-oophorectomy: a randomized, double-blind trial. J Med Assoc Thai 2009;92:1318–23.
[26] Mathiesen O, Rasmussen ML, Dierking G, et al. Pregabalin and dexamethasone in combination with paracetamol for postoperative pain control after abdominal hysterectomy. A randomized clinical trial. Acta Anaesthesiol Scand 2009;53:227–35.
[27] Eman A, Bilir A, Beyaz SG. The effects of preoperative pregabalin on postoperative analgesia and morphine consumption after abdominal hysterectomy. Acta Medica Mediterranea 2014;2014:481–5.
[28] Mao Y, Wu L, Ding W. The efficacy of preoperative administration of gabapentin/pregabalin in improving pain after total hip arthroplasty: a meta-analysis. BMC Musculoskelet Disord 2016;17:373.
[29] 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.
[30] Park IJ, Kim G, Ko G, et al. Does preoperative administration of gabapentin/pregabalin improve postoperative nasal surgery pain? Laryngoscope 2016;126:2232–41.
[31] Hamilton TW, Strickland LH, Pandit HG. A meta-analysis on the use of gabapentinoids for the treatment of acute postoperative pain following total knee arthroplasty. J Bone Joint Surg Am 2016;98:1340–50.
[32] Mishriky BM, Waldron NH, Habib AS. Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis. Br J Anaesth 2015;114:10–31.
[33] Kong VK, Irwin MG. Gabapentin: a multimodal perioperative drug? Br J Anaesth 2007;99:775–86.
[34] 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.