Review Article

Obstet Gynecol Sci 2022;65(2):133-144
https://doi.org/10.5468/ogs.21345
eISSN 2287-8580

Obstetrics & Gynecology Science

Preemptive pregabalin for postoperative analgesia during minimally invasive hysterectomy: a systematic review and meta-analysis of randomized controlled trials

Ahmed Abu-Zaid, MD[1,2], Osama Alomar, MD[1,3], Nora F AlNaim, MD[3], Fatimah Shakir Abualsaud, MD[3], Mohammed Ziad Jamjoom, MD[3], Latifa F AlNaim, MD[3], Abdullah AMA Almubarki, MD[3], Saeed Baradwan, MD[4], Saud Abdullah Saud Aboudi, MD[5], Faisal Khalid Idris, MD[3], Meshael Fodaneel, MD[3], Ismail A Al-Badawi, MD, FRCSC[1,3], Hany Salem, MD[1,3]

Department of Obstetrics and Gynecology, [1]College of Medicine, Alfaisal University, Riyadh, Saudi Arabia; [2]College of Graduate Health Sciences, University of Tennessee Health Science Center, Memphis, TN, USA; [3]King Faisal Specialist Hospital and Research Center, Riyadh; [4]King Faisal Specialist Hospital and Research Center, Jeddah; [5]College of Medicine, Prince Sattam Bin Abdulaziz University, AlKharj, Saudi Arabia

We aimed to perform a systematic review and meta-analysis of all randomized placebo-controlled trials (RCTs) that examined the analgesic benefits of preemptive pregabalin among patients undergoing minimally invasive hysterectomy. Five major databases were systematically screened from inception until August 29, 2021 Relevant studies were evaluated for risk of bias. Endpoints were analyzed using the random-effects model and pooled as the mean difference or risk ratio with a 95% confidence interval. Four studies with seven treatment arms met the inclusion criteria. The total sample size was 304 patients: 193 and 111 patients were allocated to the pregabalin and placebo groups, respectively. Overall, the included studies revealed a low risk of bias. The summary results revealed that the mean postoperative pain scores at rest were significantly lower in the pregabalin group than in the control group at 0, 2, 4, 6, 12, and 24 hours. Moreover, the mean postoperative pain scores on movement/coughing were significantly lower in the pregabalin group than in the control group at 12 and 24 hours. The rate of patients who were opioid-free postoperatively was significantly higher in the pregabalin group than in the control group. There was no significant difference between the groups in terms of the mean postoperative time to first rescue analgesic and the rates of adverse events. Compared with placebo, preemptive pregabalin was largely safe, and was correlated with superior analgesic effects in terms of lower postoperative pain scores and higher opioid-sparing effects. Additional RCTs are needed to confirm these findings.

Keywords: Pregabalin; Pain; Hysterectomy; Meta-analysis

Introduction

Vaginal, laparoscopic, and robotic hysterectomies are regarded as minimally invasive procedures [1]. They are favorably associated with better quality of life, shorter hospital stay, and lower complication rates compared with abdominal hysterectomy [2,3]. Nonetheless, severe postoperative pain remains a major concern among patients undergoing minimally invasive hysterectomy [4-6].

Opioid treatment is the mainstay of management for acute postoperative pain following minimally invasive hysterectomy [7]. Although opioids deliver optimal pain relief, they are nonetheless correlated with a number of toxicities that

Received: 2021.11.15. Revised: 2022.01.07. Accepted: 2022.02.03.
Corresponding author: Ahmed Abu-Zaid, MD
Department of Obstetrics and Gynecology, College of Graduate Health Sciences, University of Tennessee Health Science Center, 920 Madison Ave #807, Memphis, TN 38103, USA
E-mail: aabuzaid@live.com
https://orcid.org/0000-0003-2286-2181

warrant their cessation. Examples of such toxicities include constipation, nausea, vomiting, opioid addiction, drowsiness, and hypoventilation [8]. Therefore, there is a pressing demand to investigate alternative pharmacological agents that can favorably reduce patient-reported scores for postoperative pain, opioid consumption, and adverse events of multimodal analgesia.

Pregabalin belongs to the class of gabapentinoids. Structurally, pregabalin is analogous to gamma-aminobutyric acid. Functionally, it blocks the alpha-2-delta subunit of voltage-gated calcium channels that are ubiquitously expressed in the brain and spinal cord. Consequently, pregabalin blocks the release of excitatory neurotransmitters, such as norepinephrine, glutamate, and substance P. Thus, pregabalin eventually provides central and peripheral analgesic activities [9-11]. These anti-nociceptive properties have facilitated the use of pregabalin in the management of a wide array of acute and chronic pain conditions, including postoperative pain [12-17].

In the context of gynecology, a recent meta-analysis of randomized controlled trials (RCTs) concluded that preemptive administration of pregabalin was not clinically superior to placebo in terms of decreasing pain scores and opioid intake among patients undergoing abdominal hysterectomy [18]. A limited number of RCTs have investigated the efficacy of preemptive pregabalin on postsurgical pain after minimally invasive hysterectomy [19-22]. However, results of these RCTs have been conflicting and limited by small sample sizes and dissimilar doses. Notably, the different preemptive pregabalin doses resulted in inconsistent efficacy findings, warranting the need to conduct a meta-regression analysis to explore the moderating impact of preemptive pregabalin dose on the efficacy and safety endpoints. In addition, no meta-analysis to date has been performed to compile evidence and generate high-quality endorsements on the subject. Such an investigation is essential to inform evidence-based clinical decisions.

Hence, the objective of this investigation was to perform a systematic review and meta-analysis of all RCTs that examined the analgesic benefits of preemptive pregabalin among patients undergoing minimally invasive hysterectomy.

Methods

1. Protocol and registration

This investigation was carried out in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [23] and the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions [24]. Ethical approval was not required, as this investigation included previously published literature.

2. Eligibility criteria

Studies that met the following evidence-based PICOS inclusion criteria were considered appropriate: (i) patients: individuals undergoing minimally invasive hysterectomy, including vaginal, laparoscopic, and robotic approaches; (ii) intervention: preemptive pregabalin; (iii) comparator: preemptive placebo; (iv) outcomes: any of the prespecified endpoints; and (v) study design: RCTs. The exclusion criteria were as follows: (i) patients undergoing abdominal hysterectomy; (ii) interventional preemptive drugs other than pregabalin; (iii) control of preemptive drugs other than passive placebo; and (iv) study designs other than RCTs, including non-randomized studies, reviews, and conference abstracts.

3. Information sources

Five major electronic databases were screened from inception until August 28, 2021. These databases included PubMed, Web of Science, the Cochrane Central Register of Controlled Trials, Embase, and Scopus. Additionally, the reference lists of the included RCTs and recent reviews were manually screened for additional pertinent RCTs that could have been overlooked. There were no restrictions on patient age, language, or year of publication.

4. Literature search

The following query search was utilized in all five major databases: pregabalin AND hysterectomy AND (vaginal OR laparoscopic OR robotic OR minimally invasive). The literature search was independently completed by two investigators, and disagreements, if any, were rectified by consensus. Supplementary Table 1 shows the exact literature search strategy for all databases.

5. Study selection

All citations retrieved from the database search were im-

ported into an Excel spreadsheet. Duplicate citations were omitted. Next, titles and/or abstracts were screened for potential eligibility and unrelated citations were removed. Subsequently, the remaining eligible citations underwent full-text examination to determine the final eligibility for inclusion in the meta-analysis. The study selection was independently completed by two investigators, and disagreements, if any, were rectified by consensus.

6. Data collection process and items

A data collection sheet was designed to summarize the extracted data. There were two main types of data: the first type included the baseline characteristics of the included RCTs, such as study identifier, country of publication, type of minimally invasive hysterectomy, study arms, sample sizes, age/weight/height/body mass index of patients, operation time, and details of pregabalin administration. The second type of data included the following study's endpoints: (i) the mean postoperative pain scores at rest at 0, 2, 4, 6, 12, and 24 hours; (ii) the mean postoperative pain scores on movement/coughing at 12 and 24 hours; (iii) the rate of patients who were opioid-free postoperatively; (iv) the mean postoperative time to first analgesic rescue therapy in hours (intravenous tramadol 50 mg or intramuscular diclofenac sodium 1 mg/kg); (v) the rates of patients with nausea only, nausea plus vomiting, vomiting only, mouth dryness, and respiratory depression; (vi) mean Ramsay sedation score; and (vii) rate of patients with ≥3 Ramsay sedation score within 0-1 hours postoperatively [25]. The postoperative pain scores were assessed in accordance with the 10-cm visual analog scale (VAS), in which "0" corresponded to no pain at all and "10" corresponded to the worst possible pain imaginable. Postoperative opioid consumption included either pethidine (50-100 mg) or tramadol (50 mg), as reported in the relevant RCTs. Ramsay sedation score is a well-established metric used to characterize a person's level of sedation (sleepiness). It has six possible scores, as follows: patient is anxious and agitated or restless, or both (score 1); patient is cooperative, oriented, and tranquil (score 2); patient responds to commands only (score 3); patient exhibits brisk response to light glabellar tap or loud auditory stimulus (score 4); patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus (score 5); and patient exhibits no response (score 6) [25]. Data were collected by six investigators (in groups of two) independently, and disagreements, if any, were rectified by consensus among the groups.

7. Risk of bias evaluation of the included studies

The Cochrane risk of bias tool was used to assess the quality of the included studies [26]. Seven key domains were evaluated: (i) random sequence generation, (ii) allocation concealment, (iii) performance bias, (iv) detection bias, (v) attrition bias, (vi) reporting bias, and (vii) other potential sources of bias. Each domain was scored as high, low, or unclear. The risk of bias evaluation of the included studies was completed independently by two investigators, and disagreements, if any, were rectified by consensus.

8. Summary measures and data analysis

Continuous data were analyzed using the inverse variance method and summarized as mean difference (MD) with 95% confidence interval (CI). Dichotomous data were analyzed using the Mantel-Haenszel method and summarized as risk ratio (RR) with 95% CI. Considering that the effects estimated across the different RCTs were not identical, the random-effects model was used [24]. Between-study heterogeneity was defined based on two conditions: (i) the *P*-value of Cochran's Q test ($P<0.1$), and (ii) the I-square (I^2) test ($I^2>50\%$) [27]. The Review Manager Software, version 5.4.0 for Windows (Cochrane, London, UK), was used for statistical analysis of the forest plots. Leave-one-out sensitivity analysis was performed to examine the robustness of the overall findings by eliminating one study at each analysis and recalculating the overall effect sizes of the remaining studies [24]. Meta-regression analysis was performed to explore the moderator effect of preemptive pregabalin dose on all outcomes, and the results were depicted in bubble plots. Publication bias was assessed virtually through funnel plots and quantitatively using Egger's regression test [28]. The STATA software for Windows (version 17.0; StataCorp LLC, College Station, TX, USA) was used for performing leave-one-out sensitivity analysis, meta-regression analysis (bubble plots), and publication bias (funnel plots). One study [22] reported medians and range values (minimum and maximum), and the means and standard deviations were computed as outlined previously by Wan et al. [29]. Two studies [19,21] included more than one dose of pregabalin, and we treated each dose as a standalone RCT (versus control) in this meta-analysis, consistent with earlier reports [30,31].

Table 1. The baseline characteristics of the included studies

Study	Country	MIH type	Study arms (total dose)	N	Age (yr)	Weight (kg)	Height (m)	BMI (kg/m^2)	OT (minutes)	Preemptive timing
Prasad et al. [20] (2014)	India	Vaginal	Placebo	30	46.6±6.3	43.7±7.6	155.7±3.9	NR	86.2±2.4	1.5 hours before surgery
			Pregabalin (150 mg)	30	44.6±7.3	45.4±6.8	154.5±4.4	NR	88.5±1.4	
Rajappa et al. [21] (2016)	India	Vaginal	Placebo	45	47.7±9.1	NR	NR	25.9±3.9	NR	1 hour before surgery
			Pregabalin (75 mg)	45	46.7±9.9	NR	NR	24.5±3.9	NR	
			Pregabalin (150 mg)	45	46.4±10.6	NR	NR	25.1±2.6	NR	
Asgari et al. [19] (2017)	Iran	Laparoscopic	Placebo	22	44.5±6.5	73±11.4	160.2±4.6	NR	122.6±34.2	The night before surgery and 30 minutes before surgery
			Pregabalin (150 mg)	20	46.8±5.8	75.1±7.3	161.3±7.0	NR	147.5±21.5	
			Pregabalin (300 mg)	20	47.2±4.7	75±9	161.1±4.1	NR	138.8±22.9	
			Pregabalin (600 mg)	20	45.2±7.4	76.2±6.8	161.5±3.9	NR	135.5±22.4	
Sanguanwongthong et al. [22] (2019)	Thailand	Laparoscopic	Placebo	14	45.7±5.5	67.1±11.4	158.5±3.8	26.5±3.8	189.5±24.0	2 hours before surgery
			Pregabalin (150 mg)	13	43.4±4.5	60.8±11.4	159.6±4.7	23.3±3.2	191±158	

Values are presented as mean±standard deviation.
MIH, minimally invasive hysterectomy; BMI, body mass index; OT, operation time; NR, not reported.

Results

1. Literature search

Supplementary Fig. 1 summarizes the PRISMA flowchart used for the literature search. Overall, a literature search identified 102 suitable studies. After eliminating duplicate studies (n=44), the remaining studies (n=58) underwent screening of titles and abstracts, and 52 studies were excluded. Six studies underwent full-text reading, and only four unique studies were considered eligible for inclusion in the meta-analysis [19-22]. Table 1 summarizes the baseline characteristics of the included studies. Overall, this meta-analysis included four studies with seven treatment arms based on pregabalin dose. The total sample size was 304 patients. There were 193 and 111 patients allocated to the pregabalin and control groups, respectively. All studies were published between 2014 and 2019 and took place in India (n=2), Iran (n=1), and Thailand (n=1). Laparoscopic and vaginal approaches to hysterectomy were performed in two studies each. The total dose of preemptive pregabalin ranged from 75 to 600 mg.

2. Risk of bias of the included studies

Supplementary Fig. 2 summarizes the risk of bias in the included studies. Overall, the included studies revealed a low risk of bias. One study [21] did not provide adequate information about the detection bias, and this corresponding domain was scored as unclear risk.

3. Meta-analysis of the mean postoperative pain scores at rest at 0, 2, and 4 hours

The summary results revealed that the mean postoperative pain scores at rest were significantly lower in the pregabalin group than in the control group at 0 hours (n=4 RCTs; MD, -2; 95% CI, -3.38 to -0.62; *P*=0.004), 2 hours (n=4 RCTs; MD, -2.5; 95% CI, -3.51 to -1.49; *P*<0.001), and 4 hours (n=4 RCTs; MD, -1.17; 95% CI, -1.84 to -0.49; *P*<0.001). The pooled results were heterogeneous (Fig. 1).

4. Meta-analysis of the mean postoperative pain scores at rest at 6, 12, and 24 hours

The summary results revealed that the mean postoperative pain scores at rest were significantly lower in the pregabalin

Study or subgroup	Pregabalin Mean	Pregabalin SD	Pregabalin Total	Control Mean	Control SD	Control Total	Weight (%)	Mean difference IV, random, 95% CI
1.1.1 0 hours								
Asgari et al. [19] (2017) (150 mg)	3.35	0.74	20	4.86	0.71	22	24.9	-1.51 (-1.95, -1.07)
Asgari et al. [19] (2017) (300 mg)	1.95	0.6	20	4.86	0.71	22	25.0	-2.91 (-3.31, -2.51)
Asgari et al. [19] (2017) (600 mg)	1.65	0.58	20	4.86	0.71	22	25.0	-3.21 (-3.60, -2.82)
Prasad et al. [20] (2014) (150 mg)	0.39	0.56	30	0.77	0.72	30	25.2	-0.38 (-0.71, -0.05)
Subtotal (95% CI)			90			96	100.0	-2.00 (-3.38, -0.62)
Heterogeneity: Tau²=1.94; Chi²=154.23; df=3 (*P*<0.00001); I²=98%								
Test for overall effect: Z=2.84 (*P*=0.004)								
1.1.2 2 hours								
Asgari et al. [19] (2017) (150 mg)	3.1	0.44	20	4.8	0.79	22	25.5	-1.70 (-2.08, -1.32)
Asgari et al. [19] (2017) (300 mg)	1.7	0.8	20	4.8	0.79	22	24.9	-3.10 (-3.58, -2.62)
Asgari et al. [19] (2017) (600 mg)	1.15	0.81	20	4.8	0.79	22	24.9	-3.65 (-4.13, -3.17)
Prasad et al. [20] (2014) (150 mg)	4.94	1.34	30	6.48	0.63	30	24.7	-1.54 (-2.07, -1.01)
Subtotal (95% CI)			90			96	100.0	-2.50 (-3.51, -1.49)
Heterogeneity: Tau²=1.00; Chi²=56.61; df=3 (*P*<0.00001); I²=95%								
Test for overall effect: Z=4.84 (*P*<0.00001)								
1.1.3 4 hours								
Asgari et al. [19] (2017) (150 mg)	2.4	0.59	20	3.31	0.94	22	25.1	-0.91 (-1.38, -0.44)
Asgari et al. [19] (2017) (300 mg)	1.8	0.74	20	3.31	0.94	22	24.5	-1.51 (-2.02, -1.00)
Asgari et al. [19] (2017) (600 mg)	1.4	0.68	20	3.31	0.94	22	24.8	-1.91 (-2.40, -1.42)
Prasad et al. [20] (2014) (150 mg)	4.1	0.87	30	4.48	0.81	30	25.6	-0.38 (-0.81, 0.05)
Subtotal (95% CI)			90			96	100.0	-1.17 (-1.84, -0.49)
Heterogeneity: Tau²=0.42; Chi²=24.49; df=3 (*P*<0.0001); I²=88%								
Test for overall effect: Z=3.39 (*P*=0.0007)								

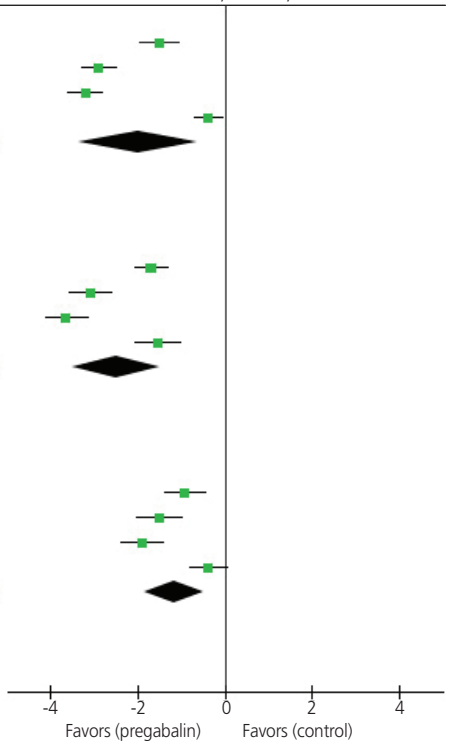

Fig. 1. Meta-analysis of the mean postoperative pain scores at rest at 0, 2, and 4 hours. SD, standard deviation; CI, confidence interval.

group than in the control group at 6 hours (n=7 RCTs; MD, -0.97; 95% CI, -1.39 to -0.55; *P*<0.001), 12 hours (n=7 RCTs; MD, -1.37; 95% CI, -2.32 to -0.42; *P*=0.005), and 24 hours (n=7 RCTs; MD, -1.23; 95% CI, -2.01 to -0.45; *P*=0.002). The pooled results were heterogeneous (Fig. 2).

5. Meta-analysis of the mean postoperative pain scores on moving/coughing at 12 and 24 hours

The summary results revealed that the mean postoperative pain scores on moving/coughing were significantly lower in the pregabalin group than in the control group at 12 hours (n=5 RCTs; MD, -1.08; 95% CI, -2.1 to -0.06; *P*=0.04) and 24 hours (n=5 RCTs; MD, -1.21; 95% CI, -2.28 to 0.15; *P*=0.03). The pooled results were heterogeneous (Fig. 3).

6. Meta-analysis of the rate of patients who were opioid-free postoperatively

The rate of patients who were opioid-free postoperatively was significantly higher in the pregabalin group than in the control group (n=5 RCTs; RR, 7.13; 95% CI, 3.72 to 13.67; *P*<0.001). The pooled results were homogeneous (Fig. 4). Sanguanwongthong et al. [22] showed that the mean postoperative opioid (fentanyl) intake was significantly lower in the pregabalin group than in the control group (133.92±77.94 vs. 337.63±178.47 mg, *P*=0.001).

7. Meta-analysis of the mean postoperative time to first rescue analgesic

The mean postoperative time to first rescue analgesic did not differ significantly between the two groups (n=3 RCTs; MD, 6.65; 95% CI, -1.04 to 14.35; *P*=0.09). The pooled results were heterogeneous (Fig. 5).

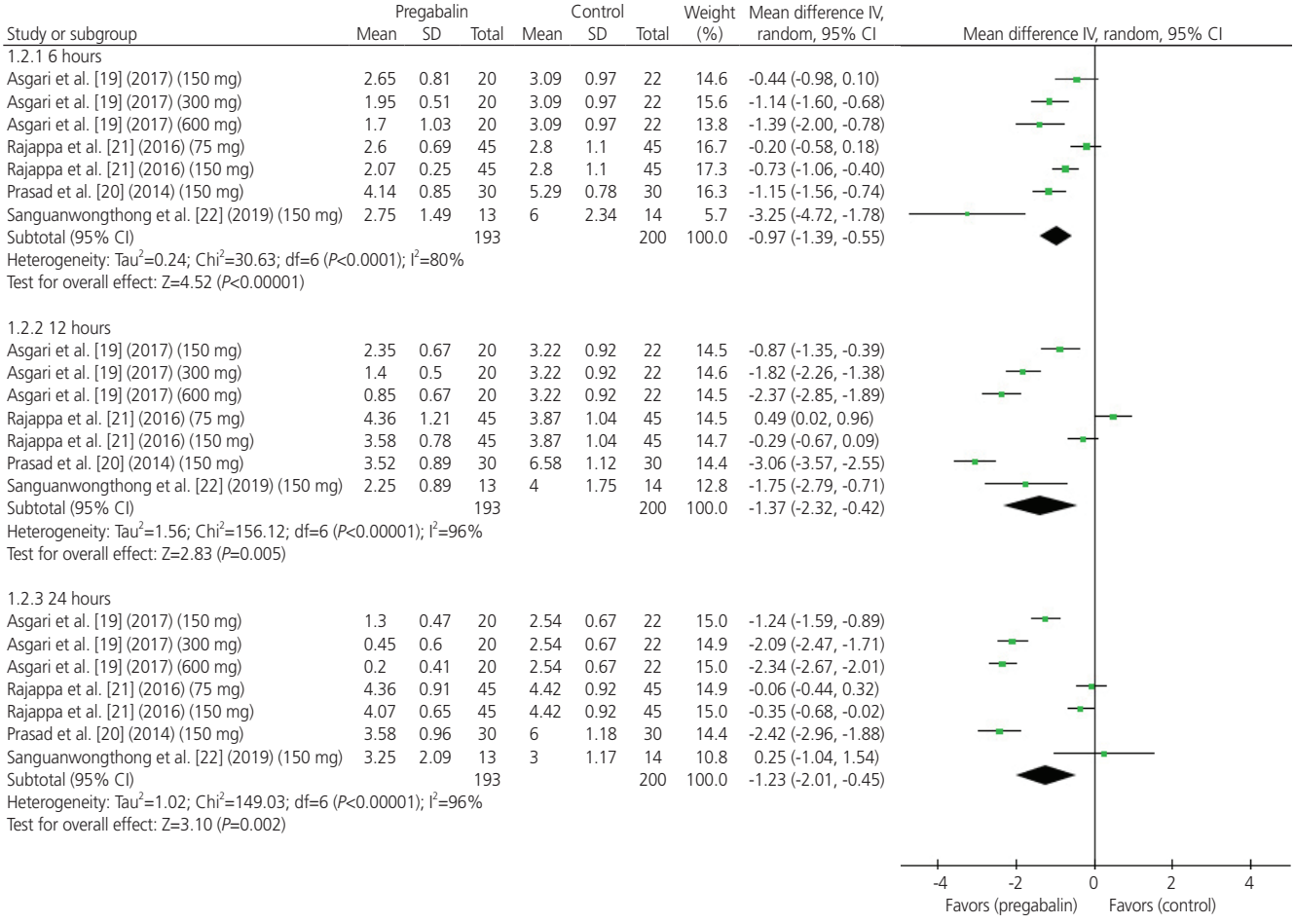

Fig. 2. Meta-analysis of the mean postoperative pain scores at rest at 6, 12, and 24 hours. SD, standard deviation; CI, confidence interval.

8. Meta-analysis of the rates of nausea only, nausea plus vomiting, vomiting only, mouth dryness, and respiratory depression

The rates of nausea only (n=6 RCTs; RR, 1.09; 95% CI, 0.98 to 1.21; *P*=0.1), nausea plus vomiting (n=4 RCTs; RR, 0.86; 95% CI, 0.44 to 1.66; *P*=0.65), vomiting only (n=2 RCTs; RR, 1.13; 95% CI, 0.73 to 1.75; *P*=0.59), and mouth dryness (n=1 RCT; RR, 2; 95% CI, 0.19 to 20.9; *P*=0.56) did not differ significantly between the two groups. The pooled results were homogeneous (Supplementary Fig. 3). One RCT by Prasad et

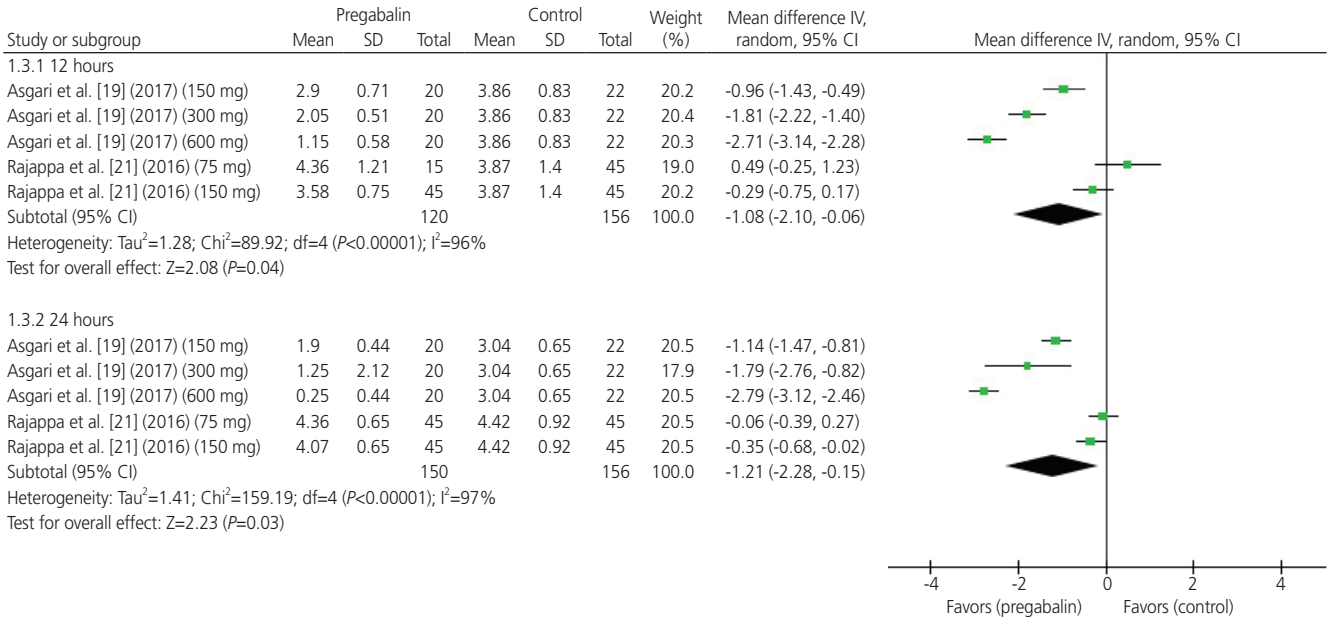

Fig. 3. Meta-analysis of the mean postoperative pain scores on moving/coughing at 12 and 24 hours. SD, standard deviation; CI, confidence interval.

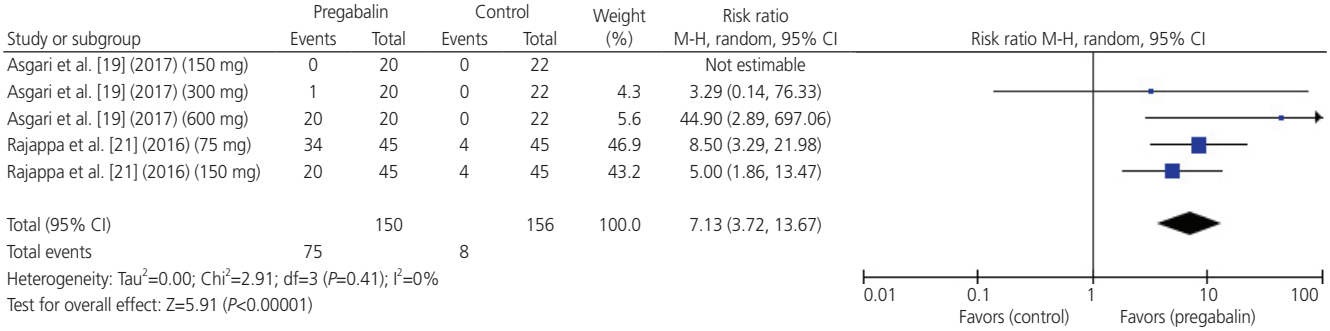

Fig. 4. Meta-analysis of the rate of patients who were opioid-free postoperatively. CI, confidence interval.

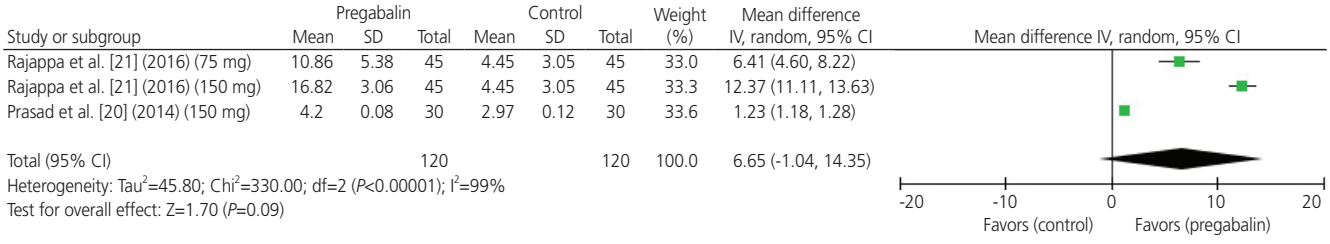

Fig. 5. Meta-analysis of the mean postoperative time to first analgesic rescue. SD, standard deviation; CI, confidence interval.

al. [20] reported respiratory depression as a potential side effect, and no single event was documented in either group.

9. Meta-analysis of the mean Ramsay sedation score and the rate of patients with ≥3 Ramsay sedation score within 0-1 hours postoperatively

The mean postoperative Ramsay sedation score did not significantly differ between the two groups (n=4 RCTs; MD, 1.04; 95% CI, -0.57 to 2.64; *P*=0.21). The pooled analysis was heterogeneous (Supplementary Fig. 4A). However, the rate of patients with ≥3 Ramsay sedation score within 0-1 hours postoperatively was significantly higher in the pregabalin group than in the control group (n=3 RCTs; RR, 16.23; 95% CI, 4.61 to 57.21; *P*<0.001). The pooled analysis was homogeneous (Supplementary Fig. 4B).

10. Leave-one-out sensitivity analysis

The results of leave-one-out sensitivity analysis demonstrated robustness for all outcomes, except for mean postoperative pain scores at rest at 0 hours, mean postoperative pain scores on motion/coughing at 12 hours, mean postoperative pain scores on motion/coughing at 24 hours, and mean postoperative time to first analgesic rescue (Supplementary Figs. 5-9). For the non-robust outcomes, omission of some individual RCTs exhibited a significant impact on the overall summary effect sizes of the rest of the RCTs.

11. Meta-regression analysis

Meta-regression based on the dose of preemptive pregabalin as a moderator showed a significant impact on the mean postoperative pain scores at rest and on motion/coughing (Supplemental Figs. 10, 11), and an inversely proportional relationship was observed in which higher preemptive pregabalin doses correlated with a greater decrease in mean postoperative pain scores. Moreover, meta-regression based on the dose of preemptive pregabalin as a moderator showed a significant impact on mean postoperative Ramsay sedation score (Supplementary Fig. 12A), and a directly proportional relationship was observed in which higher preemptive pregabalin doses correlated with a higher mean postoperative Ramsay sedation score. However, meta-regression based on the dose of preemptive pregabalin as a moderator did not show a significant impact on the other endpoints (Supplementary Figs. 12B, 13, 14).

12. Publication bias

Funnel plots and Egger's test results for all outcomes are depicted in Supplementary Figs. 15-19. Visual inspection of the funnel plots revealed no significant symmetry, except for the mean postoperative time to the first analgesic rescue and the mean postoperative Ramsay sedation score.

Discussion

This systematic review and meta-analysis examined the analgesic utility of preemptive pregabalin among patients undergoing minimally invasive hysterectomy. Four studies with seven different treatment arms were analyzed (193 and 111 patients were assigned to the pregabalin and control groups, respectively). The included studies revealed an overall low risk of bias. Our results revealed that preemptive pregabalin correlated with significantly reduced postoperative pain scores at rest and on moving/coughing. Additionally, preemptive pregabalin was associated with a higher rate of postoperative opioid-free patients. Sedation was a significant adverse event in the preemptive pregabalin group compared with the control group. There was no significant difference between the groups regarding the rates of other adverse events, and these adverse events tended to increase with higher doses.

Preemptive analgesia has the advantage of preventing the onset of nociceptive stimuli and decreasing the degree of postoperative pain [32]. Pregabalin has anxiolytic, anticonvulsant, and most importantly, analgesic properties [10,12]. High-quality evidence from meta-analyses of RCTs demonstrated the analgesic efficacy of preemptive pregabalin in decreasing postsurgical pain score and opioid consumption among patients undergoing surgery for breast cancer [14], total joint arthroplasty [15], thoracotomy [16], and laparoscopic cholecystectomy [33]. The present meta-analysis echoes the aforementioned studies and corroborates the analgesic utility of preemptive pregabalin in controlling postoperative pain and minimizing opioid intake among patients undergoing minimally invasive hysterectomy. Our findings are in opposition to a meta-analysis that demonstrated no analgesic advantages of preemptive pregabalin among patients undergoing abdominal hysterectomy [18]. One potential reason for this observed conflict could be ascribed to the fact that minimally invasive hysterectomy is associated with less trauma to the body than abdominal hysterectomy, in terms

of less incisional injury, inflammation, and neuropathic insult [34]. Hence, pain perception is anticipated to be intrinsically lower in minimally invasive hysterectomy than in abdominal hysterectomy. Therefore, preemptive pregabalin is projected to exhibit more analgesic benefits among patients undergoing minimally invasive hysterectomy than those undergoing abdominal hysterectomy.

Poor control of postoperative pain is associated with a number of unfavorable outcomes. Such outcomes include increased chronic opioid addiction, delayed mobilization, poor quality of life, prolonged hospitalization, delayed return to normal activities, higher hazard of postoperative complications, and increased patient care expenses [5]. The minimum clinically important difference for alleviation of acute postoperative pain is a reduction of at least 1 point out of the 10-point VAS [35]. Our meta-analysis showed that the reductions in postsurgical pain scores at rest and on motion/coughing were statistically significant and clinically important. Higher analgesic benefits, in terms of postoperative pain scores and opioid-sparing effects, were observed at higher doses, suggesting a dose-response relationship. This phenomenon was previously reported in a network meta-analysis of 79 RCTs [36].

Sedation was a significant adverse event of preemptive pregabalin in our meta-analysis, which is consistent with previous literature [37]. Moreover, our meta-analysis revealed no significant toxicity of pregabalin compared with the control regarding the rates of nausea only, vomiting only, nausea plus vomiting, mouth dryness, and respiratory depression. However, the abovementioned toxicities tended to increase with higher doses, suggesting a potential dose-dependent correlation [36]. Thus, the analgesic benefits of preemptive pregabalin should be carefully balanced against anticipated toxicities.

Gabapentin is a gabapentinoid drug that is closely related to pregabalin [9,10]. A recent meta-analysis of RCTs (n=14) demonstrated the analgesic efficacy of preemptive gabapentin among patients undergoing hysterectomy [38]. Overall, 12 and two RCTs involved patients undergoing abdominal and minimally invasive hysterectomy, respectively. The study concluded that administration of preemptive gabapentin correlated with reduced postoperative pain scores, better opioid-sparing sparring effects, higher patient satisfaction, and lower incidence rates of nausea and vomiting. Nonetheless, the clinical utility and safety of preemptive gabapentin have yet to be comprehensively evaluated among patients undergoing minimally invasive hysterectomy.

Prospective investigations may include conducting RCTs comparing pregabalin with active comparators (for example, gabapentin or para-cervical block with bupivacaine) [39] among patients undergoing minimally invasive hysterectomy. The optimal dose of preemptive pregabalin has yet to be determined. Thus, additional studies may involve conducting a dose-response analysis to identify the preemptive pregabalin dose that will achieve the maximum analgesic effect and minimum toxicity. Furthermore, it will be of interest to identify the subset of patients who are likely to gain maximum benefit from preemptive pregabalin during minimally invasive hysterectomy. Lastly, future investigations may include examining whether pregabalin administered preemptively and postoperatively will correlate with better analgesia compared with preemptive administration only.

In this meta-analysis, the data on publication bias should be interpreted with extreme caution for three main reasons. First, funnel plots were assessed subjectively; hence, the results were liable to underestimation or overestimation of publication bias [40]. Second, it remains uncertain whether funnel plots can properly identify publication bias [41]. Third, when the total number of included studies is less than 10 RCTs per outcome, the visual inspection of funnel plots and their quantitative methods (for example, Egger's regression test) become unreliable [28,42].

Our investigation has a number of strengths that should be acknowledged. We performed the first meta-analysis to scrutinize the analgesic efficacy and safety of preemptive pregabalin among patients undergoing minimally invasive hysterectomy. We conducted PRISMA-compliant research, screened five major databases, and applied strict eligibility criteria. As opposed to other study designs, we considered only RCTs to facilitate the generation of high-quality evidence. Quality assessment of the eligible RCTs exhibited an overall low risk of bias, highlighting the validity of the conclusions. Additionally, we reported several endpoints and dissected the pregabalin doses. Lastly, we enriched our investigation with leave-one-out sensitivity analysis, meta-regression analysis, and funnel plot assessment for publication bias for all outcomes.

Nonetheless, our investigation also has some limitations. These limitations include the relatively small number of eligible RCTs and their corresponding small sample sizes. Moreover, in most of the comparisons, data were analyzed from

only two studies. Both limitations may have played key roles in the observed between-study heterogeneity of the reported outcomes. Additional limitations include the different patient demographics (for example, type of minimally invasive hysterectomy) and pregabalin administration (for example, the variance of dose and schedule), which could have impacted the reported endpoints and culminated in higher between-study heterogeneity. Moreover, the included RCTs failed to document other relevant endpoints, such as hospitalization length, chronic pain control at three months, patient satisfaction, and rapidity of return to normal activities.

Conclusion

Among patients undergoing minimally invasive hysterectomy, preemptive pregabalin was safe and correlated with superior analgesic effects in terms of lower postoperative pain scores and higher opioid-sparing effects compared with placebo. Owing to the unavoidable limitations of this meta-analysis, the conclusions should be interpreted with caution, and additional RCTs are needed to validate these findings.

Conflict of interest

The authors declare that they have no conflicts of interest.

Ethical approval

This study does not require approval of the Institutional Review Board because no patient data is contained in this article. The study was performed in accordance with the principles of the Declaration of Helsinki.

Patient consent

Written informed consent and the use of images from patients are not required for the publication.

Funding information

None.

Supplementary material

Supplementary Table 1 and Figs. 1-19 associated with this article can be found online at https://doi.org/10.5468/ogs.21345.

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