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Review Article

Preoperative single dose of pregabalin alleviates postoperative pain: systematic review and meta-analysis

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Abstract: Purpose: The aim of this meta-analysis is to probe the impact of preoperative single dose of pregabalin on postoperative pain. Methods: PubMed, Embase and Cochrane library were searched for randomized controlled trials investigating preoperative single dose of pregabalin for postoperative analgesia. Pain scores at rest, opioid consumption and adverse effects were assessed in our meta-analysis. Findings: Eighteen trials with 1224 patients were finally included in our meta-analysis. Studies indicated that pre-emptive pregabalin significantly reduced the postoperative pain scores (SMD, -0.41, 95% CI: -0.72 to -0.11) and postoperative opioid consumption (SMD, -1.76, 95% CI: -2.27 to -1.26). In analysis of subgroups by different doses, 300 mg of pregabalin showed reduction of pain scores at rest (SMD, -0.51, 95% CI: -0.94 to -0.08) whereas 75 mg and 150 mg of pregabalin did not. In addition, 150 mg and 300 mg pregabalin reduced the opioid consumption significantly (SMD, -1.47, 95% CI: -2.07 to -0.87, SMD, -2.10, 95% CI: -2.98 to -1.22, respectively). Static pain scores decreased at 24 h in the thoracic and abdominal surgeries (SMD, -0.48, 95% CI: -0.95 to -0.01) and the ENT surgeries (SMD, -0.91, 95% CI: -1.60 to -0.23) rather than in the gynecological or orthopedic surgeries. Preoperative pregabalin significantly diminished the postoperative opioid consumption in orthopedic surgeries (SMD, -1.32, 95% CI: -2.22 to -0.42) and thoracic and abdominal surgeries (SMD, -2.21, 95% CI: -2.98 to -1.44) but did not show remarkable reduction of postoperative opioid consumption in ENT surgeries (SMD, -0.36, 95% CI: -0.87 to 0.15) or gynecological surgeries (SMD, -1.70, 95% CI: -4.06 to 0.66). The side effects were limited to the first postoperative 24 h. Pregabalin decreased the risk of PONV (RR, 0.60, 95% CI: 0.41 to 0.88) and nausea (RR, 0.61, 95% CI: 0.38 to 0.99) but not visual disturbance, sedation, vomiting, dizziness, headache or respiratory depression. Conclusions: This current meta-analysis suggested that pregabalin could attenuate postoperative pain and reduce opioid consumption compared to placebo but not in all doses or surgeries.

Keywords: Pregabalin, meta-analysis, postoperative pain, analgesia

Introduction

The development of postoperative pain is an unpleasant sensory of surgery that seriously affects the patients' life quality. Postoperative pain is the main reason of the extended convalescent and the dominating complaint. Recent advances in the pathophysiology of pain have suggested that it is possible to prevent or attenuate the central neural hyper-excitability, which could contribute to the enhanced postoperative pain. Clinically, the acute postoperative pain sometimes transforms into chronic pain. In the past decades, although the acute pain physiology has been mostly understood, about 80% of surgery patients suffered postoperative pain [1].

In recent years, numerous articles have reported that preoperative use of gabapentin or pregabalin could effectively alleviate postoperative pain. As a successor of gabapentin, pregabalin

Table 1. Review data extraction criteria

Participant characteristics	Intervention	Comparison	Outcomes
◊ First author (Year)	◊ PGB dose	◊ Control group	◊ Primary outcome
◊ Origin country	◊ Time of PGB		◊ Follow-up duration
◊ Trial: Control	Administration		◊ Adverse effects
◊ Surgery type			
◊ Anesthesia type			
◊ Postoperative analgesia			

PGB: pregabalin.

which is a gamma-amino-butyric acid analogue binding the $\alpha_2\delta$ subunits of the voltage-gated calcium channels and is often used to treat neuropathic pain [2]. Compared with gabapentin, pregabalin which is used as anticonvulsant, anti-hyperalgesic, and anxiolytic drug for its better pharmacokinetic profile and absorbance rate [3]. Pregabalin could reduce the hyperexcitability of dorsal horn neurons induced by tissue damage, therefore it may be useful in the postsurgical pain prevention [4, 5]. However, due to the contradicting clinical study results, there are no definitive guidelines for the use of pregabalin in the management of postoperative pain. Accordinglly, a Cochrane review in 2007 showed that the effect of pregabalin on preventing acute postoperative pain is inconclusive [6]. Hence, the use of the pregabalin for acute postoperative pain is still off-label though widely reported [7].

In 2014, a meta-analysis published in British Medical Journal (BMJ) suggested that pregabalin could improve postoperative analgesia [8]. However, the result is not convincible since it included multiple drug administration, which may distort the assessment of analgesic effect such as complex medication and monotherapy as well as single-dose and multiple-dose administration. Therefore, we performed this systematic review to provide a meta-analysis of the prevention of postoperative pain by using a preoperative single dose of pregabalin. This study investigated whether the outcomes depended on individual pregabalin dose, type of anesthesia, or surgical type. In addition, it also evaluated the impact of pregabalin administration on adverse effects.

Methods

We complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations (PRISMA guidelines) [9] and used a priori published protocol [7].

Search strategy

We searched the studies of randomized placebo controlled trails published before December 2014 in PubMed, Embase and Cochrane library databases. The keywords 'Pregabalin', 'Lyrica' and the MESH terms: 'postoperative', 'pain, postoperative', 'pain, acute' were used when searching the databases. In addition, we manually searched the reference lists of relevant articles to locate additional studies.

Eligibility criteria and data extraction

This study only included previously published clinical trials in English when they met the following criteria strictly:

Patients: Adults over the age of 18 undergoing surgical procedures not limited by age and sex.

Intervention: Using a single dose of pregabalin before operation.

Comparison: Using placebo in the control group.

Outcomes: pain scores at rest and during movement, opioid consumption and/or adverse effects.

All the reviews, letters to the editor, comments or meta analyses were not included in this study.

All studies must follow the provisions of ethics committee and patients without gender restrictions were eligible for American Association of Anesthesiology classification (ASA) I-III. Anesthesia of all studies included was general anesthesia.

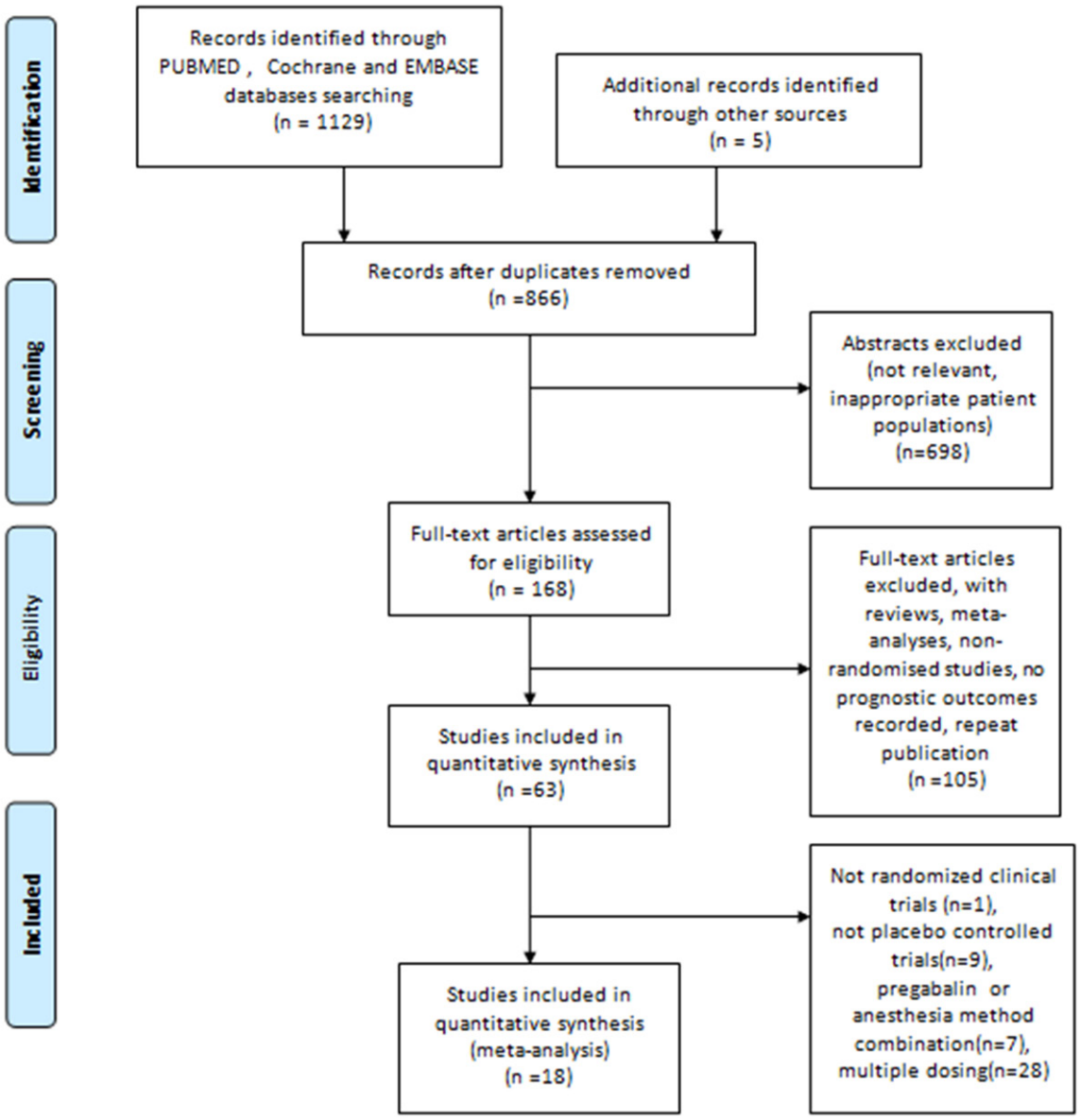

Figure 1. Study flow diagram, following PRISMA criteria with modifications.

Two authors (D.F. and J.W.) separately assessed eligibility of the articles based on the criteria (**Table 1**). They also used the risk of bias table (NIHR-CRD) suggested by the Cochrane Collaboration to assess each trial's risk of bias [10]. Papers with insufficient data were included only if the authors provided us with the original materials after inquiry. The divergences between the two authors were promptly resolved by consulting among all of the authors.

Outcomes and data analysis

This meta-analysis was performed by evaluating the impact of a single dose of pregabalin on acute postoperative pain. The main outcomes measured were pain scores, total opioid consumptions and the incidence of side effects. The Visual Analogue Scale (VAS) scores or Number Rating score (NRS) was used to evaluate pain scores. VAS scores system or NRS scores system used in all studies was converted to a 0-10 scale where zero meaned no pain and 10 indicated worst imaginable pain.

The conversion of analgesic efficiency among various opioids was established based on extensive literature review. Here, postoperative opioid consumption was transformed into morphine consumption. The analgesic potency of

Table 2. Characteristics of included studies

First author (Year)	Origin county	trial: control	Surgery type	PGB dose	Time of PGB Administrati-on	Postoperative analgesia	Outcome measures	Follow-up duration	Adverse effects
Agarwal, A [60] (2008)	India	27:29	laparoscopic cholecystectomy	150 mg	single dose: 1 h before surgery	i.v. PCA fentanyl	pain scores; opioid consumption	24 h	Postoperative nausea and vomiting (PONV); Headache; sedation; respiratory; depression;
Akarsu, T [61] (2012)	Turkey	30:30	laparoscopic cholecystectomy	300 mg	single dose: 1 h before surgery	a single 75 mg of dose intramuscular diclof-enac sodium was given to Group C patients 15-20 minutes before the estimated time of surgery	pain scores; opioid consumption MMT	24 h	Postoperative; nausea; vomiting; headache; sedation; respiratory depression; visual; disturbance; dizzy
Alimian, M [62] (2012)	Iran	40:40	Dacryocystorhi-nostomy Surgery	300 mg	single dose: 1 h before surgery	if the pain score ≥3, i.v.25 mg pethidine	pain scores; nau-sea and vomiting	24 h	nausea and vomiting
Aydogan, H [73] (2013)	Turkey	30:30	percutaneous nephrolithotomy	75 mg	single dose: 1 h before surgery	i.v. PCA morphine	pain scores; opioid consumption; CrCl; NGAL; cystatin C pain scores; opioid consumption; sedation;	24 h	nausea, vomiting pruritus, urinary, retention; somnolence, dizziness, vision; abnormalities (double or blurred) and head-ache
Balaban, F [63] (2011)	Turkey	60 (300 mg:150 m =30:30):30	laparoscopic cholecystectomy	150 mg; 300 mg	single dose: 1 h before surgery	if the pain score ≥5, i.v. 25 μg fentanyl		24 h	nausea, vomiting, pruritus, and urinary retention
Bornemann-Cimenti, H [81] (2012)	Austria	13:13	transperitoneal nephrectomy	300 mg	single dose: 1 h before surgery	PCA piritramide	opioid consump-tion; normalized area of hyperalge-sia; NRS	48 h	PONV
Cabrera Schulmeyr, MC [64] (2010)	Chile	39:41	Laparoscopic Sleeve Gastrec-tomy	150 mg	Single dosing: 2 h before surgery	Infusion of ketoprofen 300 mg 24 h^{-1}+i.v. morphine as rescue therapy	pain scores; opioid consumption; nau-sea and vomiting	24 h	PONV
Demirhan, A [65] (2014)	Turkey	30:30	Septoplasty	300 mg	single dose: 1 h before surgery	PCA tramadol HCl	pain scores; opioid consumption; sedation, dizziness, nausea	24 h	nausea, vomiting, dizziness, blurred, vision, headache, loss of concentration, itching
Ghai, A [75] (2011)	India	30:30	abdominal hysterectomy	300 mg	Single dosing: 1-2 h before surgery	I.M. diclofenac sodium; i.v. tramadol if pain not controlled	opioid consump-tion; sedation; dizziness; nausea, vomiting	24 h	Sedation; dizziness nausea, vomiting
Gonano, C [66] (2011)	Austria	20:20	minor orthopae-dic surgery	300 mg	Single dosing: at least 1 h before surgery	PACU: i.v. piritramide; after PACU: oral mef-enamic acid	pain scores; opioid consumption	24 h	Not reported
Hegarty, DA [1] (2011)	Ireland	14:18	Lumbar Discec-tomy	300 mg	Single dosing: at least 2 h before surgery	PACU: i.v. morphine; PCA: paracetamol 6 h for 24 h	nausea; vomiting dizziness blurring of vision	24 h	nausea, somnolence, light-headedness headache, dizziness, visual, disturbances, and vomiting

Paech, MJ [69] (2007)	Austra-lia	45:45	minor gyneco-logical surgery	100 mg	single dose: 1 h before surgery	PACU: i.v. fentanyl then i.v. tramadol followed by oral diclofenac if target pain score not achieved. After discharge: paracetamol as needed	Pain scores, opioid consumption, sedation score, headache, light-headedness, visual, difficult-walking	24 h	headache, light-headedness visual, disturbance difficulty walking
White, PF [72] (2009)	America	27 (75 mg):27 (150 mg); 27 (300 mg):27 (placebo)	Otolaryngology; General surgery; Plastic surgery; Urologic surgery	75 mg 150 mg 300 mg	60 min before surgery	fentanyl 233 ug (intra-operation + postopera-tive); Remifentanil 1000 ug (intraoperation)	sedation scores; pain scores; opioid consumption	2 h	dizzy or light headache, nausea and vomiting; over sedation
Srivastava, K [76] (2014)	India	30:30	spine surgery	150 mg	single dose: 1 h before surgery	i.v. PCA fentanyl	Incidence and severity of CRBD; Opioid consumption; sedation score	6 h	CRBD
Spreng, UJ [71] (2011)	Norway	22:24	lumbar discec-tomy	150 mg	single dose: 1 h before surgery	i.v. PCA morphine	pain scores; opioid consumption; side-effects, pre-operative anxiety	24 h	nausea; vomiting; sedation; Dizziness; Pruritus, Urinary, retention; Respiratory depression; Headache;
Sagit, M [70] (2013)	Turkey	96 (75 mg:150 mg=50:46):47	septoplasty	75 mg; 150 mg	single oral dose: 1 h before surgery	IM Diclofenac	pain scores; opioid consumption	24 h	PONV, dizziness
Lee, C [67] (2013)	Korea	31:29	laparoendo-scopic single-site urologic surgery	300 mg	single oral dose: 1 h before anes-thesia	i.v. PCA morphine	pain scores; opioid consumption; mechanical hyper-algesia;	24 h	Somnolence; Dizziness, Dry mouth; Blurred vision; PONV
Martinez, V [68] (2014)	France	35:38	total hip arthro-plasty	150 mg	single dose:1 h before surgery	i.v. PCA morphine	pain scores; opioid consumption	48 h	Nausea; Vomiting; PONV; Sedation score; Pruritus; Dizziness; Nightmare; Hallucinations; Voiding; difficulties; Urinary, retention;

PGB, pregabalin; GA, general anesthesia; i.v, intravenous injection; PCA, patient controlled analgesia; PONV, postoperative nausea and vomiting; MMT, mini mental test; Group C, Group of control; CrCL, creatinine clearance; Cysl, cystatin; NGAL, blood neutrophil gelatinase-associated lipocalin; NRS, numerical rating scale; CRBD, catheter related bladder discomfort.

Table 3. Quality evaluation

Study (Year)	Randomization	Treatment allocation concealed?	Similar groups at baseline?	Specified eligibility criteria?	Outcome assessor blinded?	Care provider blinded?	Patient blinded?	Point Estimates of variability for primary outcome measures?	Intention-to-treat analysis for post-operative outcomes?	Total quality score /9
Agarwal, A (2008)	Y	Y	Y	Y	Y	Y	Y	Y	N	8
Akarsu, T (2012)	N	?	Y	Y	?	N	Y	Y	N	4
Alimian, M (2012)	Y	Y	Y	Y	?	Y	Y	Y	N	7
Aydogan, H (2014)	Y	Y	Y	Y	Y	Y	Y	Y	N	8
Balaban, F (2011)	Y	Y	Y	Y	?	Y	Y	Y	N	7
Bornemann-Cimenti, H (2012)	Y	Y	Y	Y	Y	Y	Y	Y	N	8
Cabrera Schulmeyer, MC (2010)	Y	Y	Y	Y	?	Y	Y	Y	N	7
Demirhan, A (2014)	Y	Y	Y	Y	Y	Y	Y	Y	N	8
Ghai, A (2011)	Y	Y	Y	Y	Y	Y	Y	Y	N	8
Gonano, C (2011)	Y	?	Y	Y	Y	Y	Y	Y	N	7
Hegarty, DA (2011)	Y	Y	Y	Y	Y	Y	Y	Y	N	8
Paech, MJ (2007)	Y	Y	Y	Y	Y	Y	Y	Y	N	8
White, PF (2009)	Y	Y	Y	Y	Y	Y	Y	Y	N	8
Srivastava, VK (2014)	Y	Y	Y	Y	?	Y	Y	Y	N	7
Spreng, UJ (2011)	Y	Y	Y	Y	Y	Y	Y	Y	N	8
Sagit, M (2013)	Y	?	Y	Y	Y	Y	Y	Y	N	7
Lee, C (2013)	?	?	Y	Y	?	?	?	Y	N	3
Martinez, V (2014)	Y	Y	Y	Y	Y	Y	Y	Y	N	8

?, Not reported or Unclear; N, NO; Y, YES.

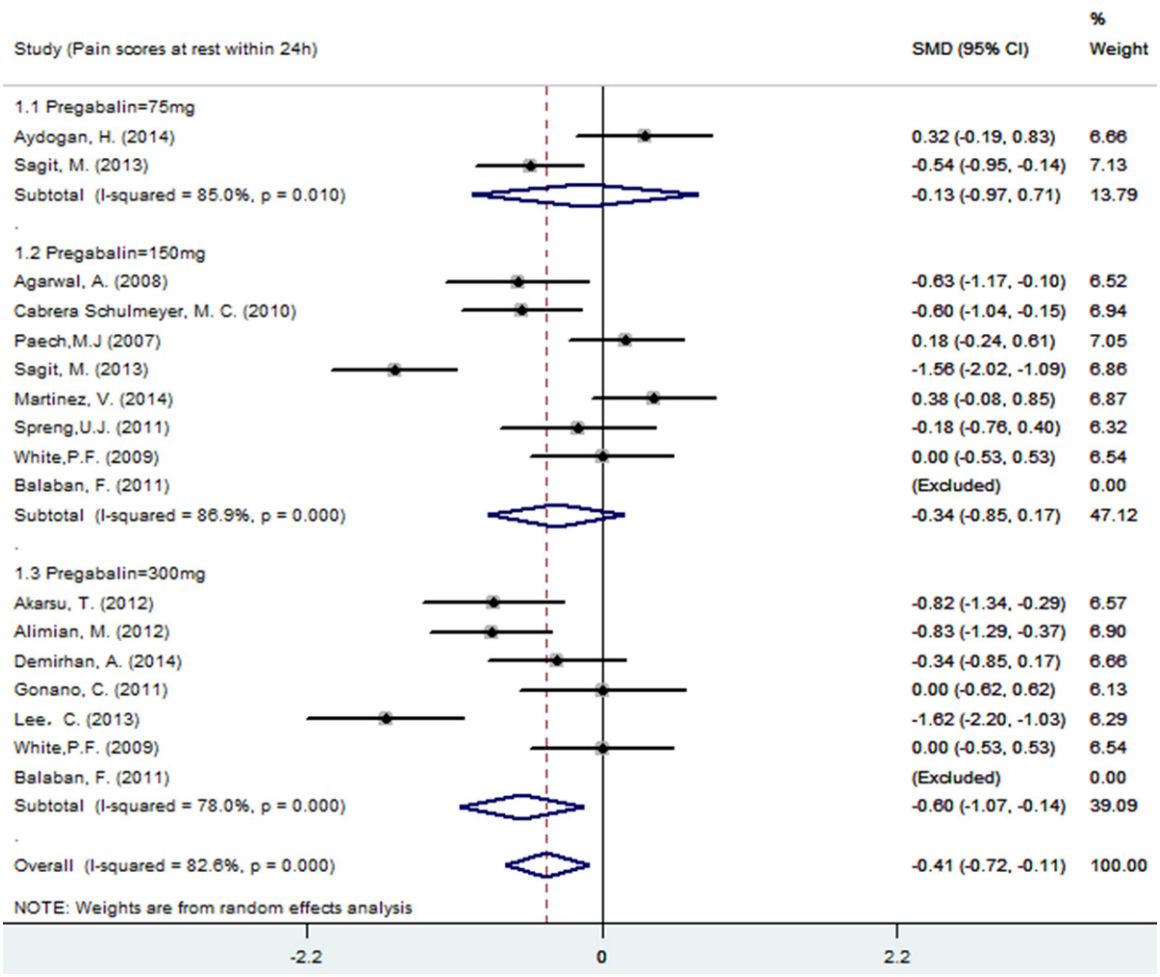

Figure 2. Pain scores at rest within 24 h by the dose of pregabalin. SMD, standardized mean difference; CI, confidence interval.

tramadol is about 10% of morphine following parenteral administration [11, 12]. The conversions between pethidine and morphine are: The analgesic potential of pethidinetimes 0.1 equals to morphine via oral route and times to 0.133 via parenteral route [12]. The analgesic potency of nalbuphine is equivalent to morphine [12]. Morphine was used in a conversion factor of 3:1 for oxycodone [13], 0.15:1 for parenteral hydromorphone [13]. Ketorolac provides comparable analgesia to morphine [14], with 100 ug of fentanyl equivalent in analgesic effect to 10 mg of morphine [13]. If the data were not reported at the time points in this analysis, we replaced it with the data near the point in time.

We analyzed data of the included trials by using standard software (Stata version 12.0). We used the I^2 statistics to evaluate heterogeneity. I^2 statistic is the percentage of total variation among the studies described. If heterogeneity was large, a random-effect model was used otherwise a fixed-effect model was used. The adoption of subgroup analysis was gauged by evaluation of the heterogeneity. Substantial heterogeneity led to a prespecified subgroup analyzed by the category such as the type of surgeries, the mode of administration, and the dose of pregabalin. Sensitivity analysis was done for analyzing the sources of heterogeneity. We performed a sensitivity analysis for pain scores at rest.

We did subgroups analysis of this meta-analysis to illuminate whether the pregabalin dose or type of surgery influence the effect of acute postoperative pain. The single dose of pregabalin in all studies was categorized into three levels as subgroups (75 mg, 150 mg, and 300 mg).

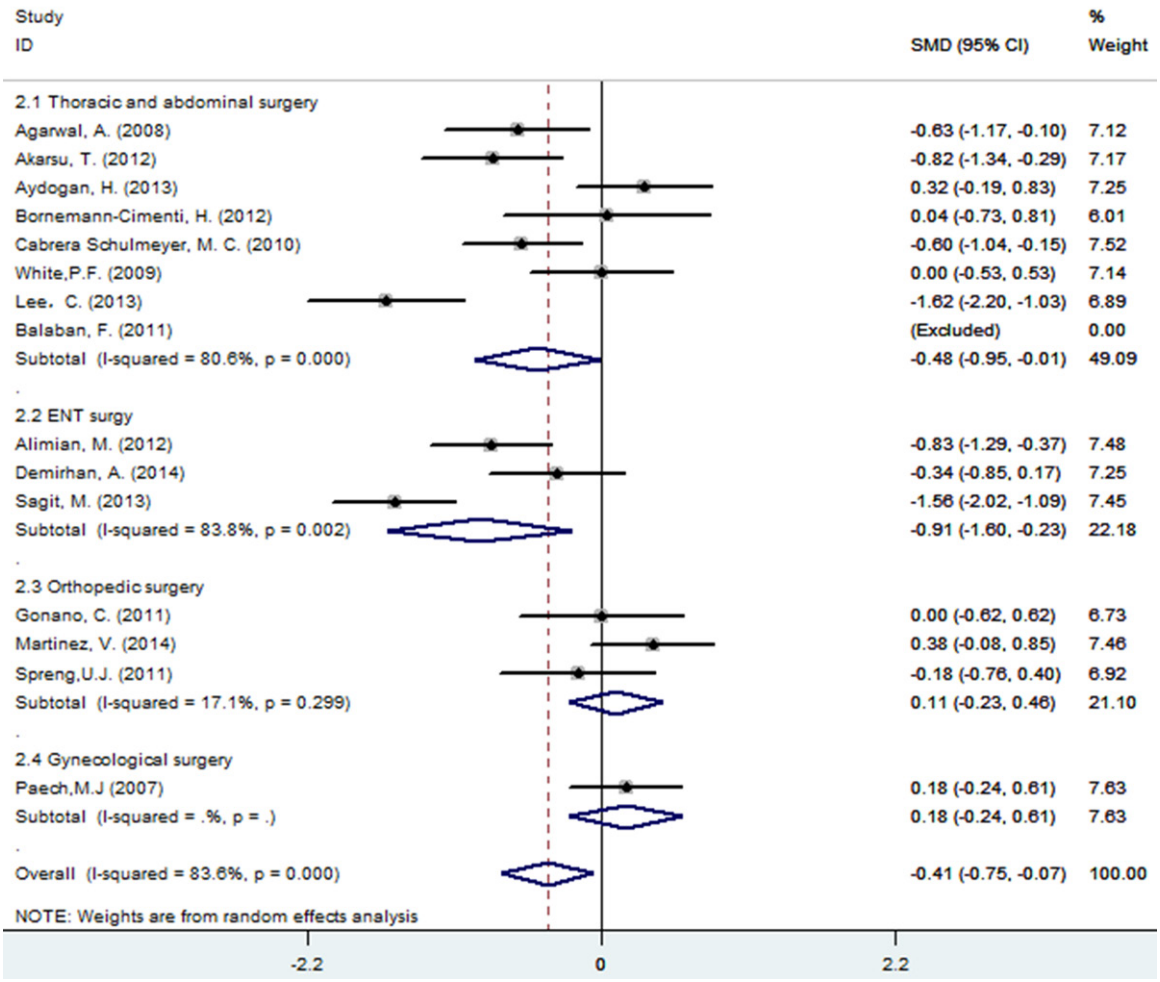

Figure 3. Analysis of pain scores at rest by the surgery type.

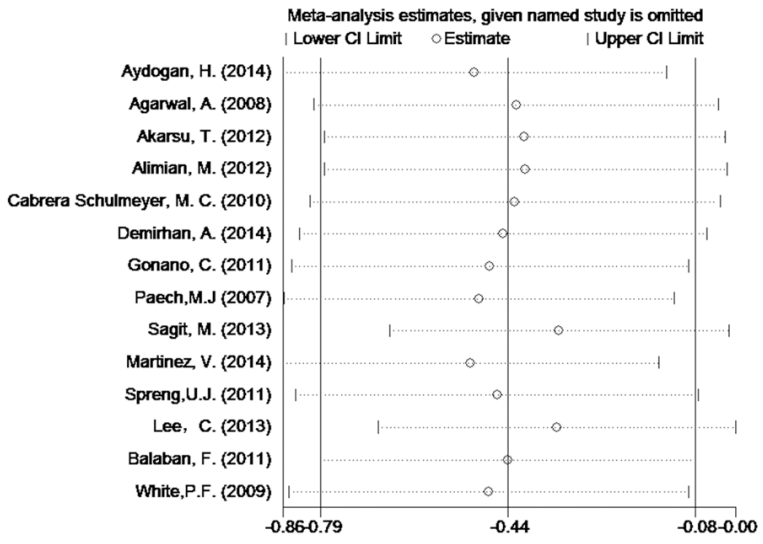

Figure 4. Sensitivity analysis of static pain scores. CI, confidence interval.

Results

Among a total number of 1134 references identified by electronic and manual searches, 168 references require full text review. After review, 104 studies were excluded for various reasons: 3 repeated publications, 15 meta-analyses, 10 papers without prognostic outcomes recorded, 21 insufficient data for analysis, 56 letters, comments and reviews. The other 64 articles are excluded as following: non-randomized clinical trials [15], not placebo controlled trials [16-24], complicated anesthesia

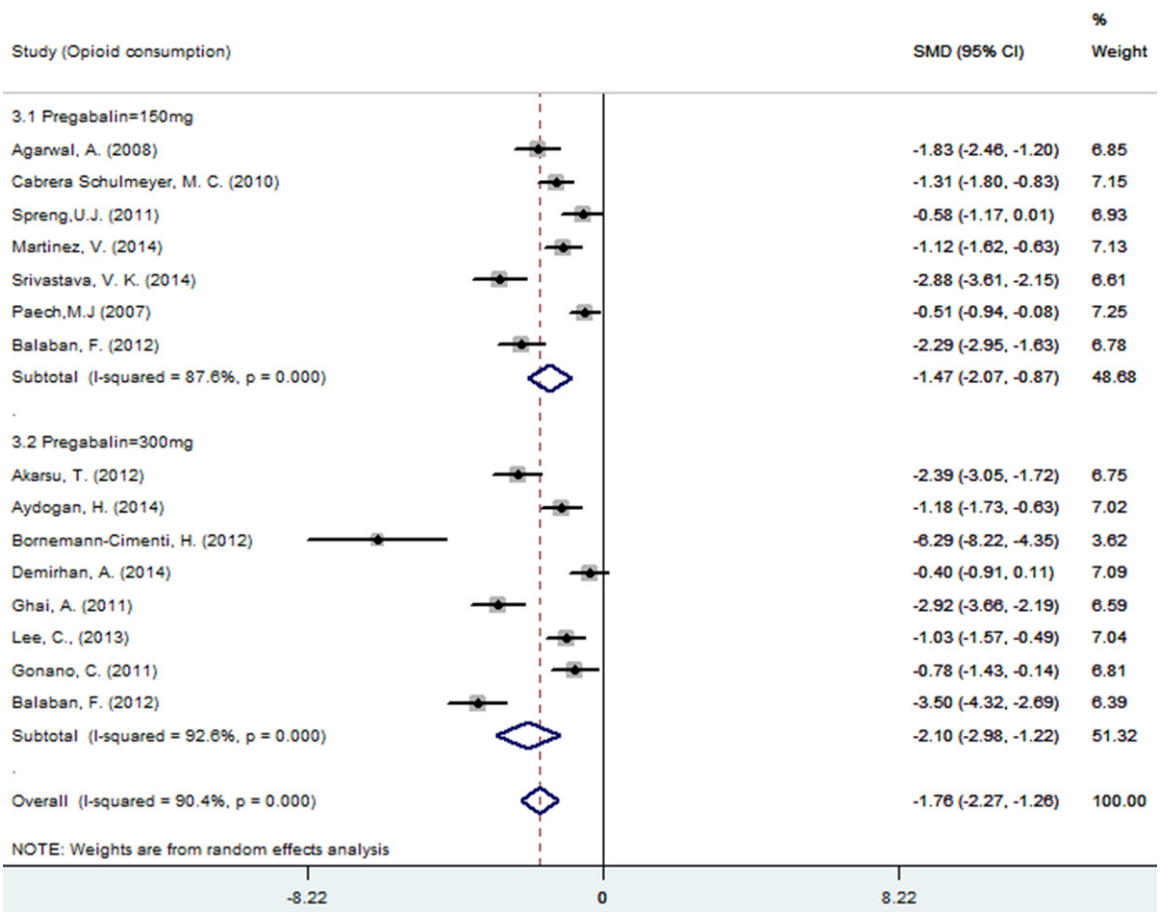

Figure 5. Analysis of the opioid consumptions by the dose of pregabalin.

methods in combination of paravertebral block and general anesthesia [25], multiple dosing (the studies performed at least one dose of pregabalin except for the preoperative dose or more than one preoperative dose) [26-53] and different anesthesia methods among groups [54-57], pregabalin combination [58, 59]. Finally, we included 18 randomized controlled trails enrolling a total of 1224 patients (**Figure 1**).

The baseline characteristics were summarized in **Table 2** with 551 (45.0%) participants receiving placebo and 673 (55.0%) participants receiving pregabalin. The baseline characteristics involved in the dose of pregabalin, the time of drug administration, follow-up duration, surgery type and the primary outcomes. **Table 3** showed the risk of bias of the included studies.

Pain scores

Static pain scores within postoperative 24 h (**Figure 2**) were investigated in 14 studies [60-73]. Pooled results showed that compared with placebo group, pre-emptive pregabalin significantly reduced the post-operative pain scores (SMD, -0.41, 95% CI: -0.72 to -0.11). Pain scores at movement were not analyzed due to insufficient sample number. By subgroup analysis, pregabalin dose of 300 mg showed acute postoperative analgesic effect (SMD, -0.51, 95% CI: -0.94 to -0.08) while pregabalin dose of 150 mg and 75 mg did not display significant analgesic effect (SMD, -0.34, 95% CI: -0.85 to 0.17, SMD, -0.13, 95% CI: -0.97 to 0.71, respectively). Meanwhile, pain scores were reduced in the thoracic and abdominal surgeries (SMD, -0.48, 95% CI: -0.95 to -0.01) and the ENT surgeries (SMD, -0.91, 95% CI: -1.60 to -0.23) but

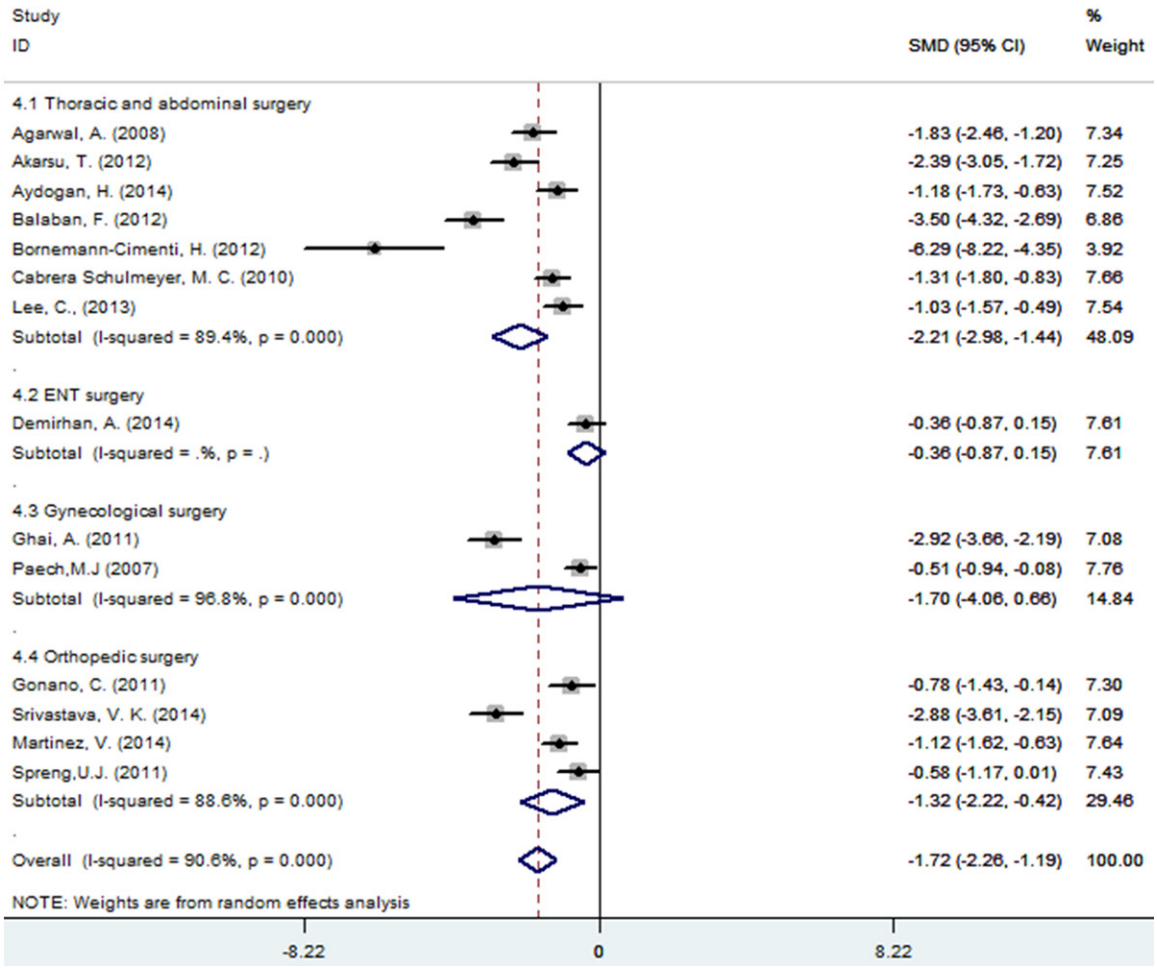

Figure 6. Analysis of the opioid consumptions by surgery type.

not in the gynecologic surgeries (SMD, 0.18, 95% CI: -0.24, 0.61) or orthopedic surgeries (SMD, 0.11, 95% CI: -0.23, 0.46) (**Figure 3**, **Table 4**). Additionally, sensitivity analysis suggested no difference in the static pain scores (**Figure 4**).

Opioid consumption

A total of 14 studies [60, 61, 63-69, 71, 73-76] were included to analyze the postoperative opioid consumption. Pooled results showed that pre-emptive pregabalin could significantly reduce the postoperative opioid consumption compared with placebo group (SMD, -1.76, 95% CI: -2.27 to -1.26). In addition, postoperative opioid consumptions were diminished by preoperative pregabalin 150 mg and 300 mg when analyzed alone (SMD, -1.47, 95% CI: -2.07 to -0.87, SMD, -2.10, 95% CI: -2.98 to -1.22, respectively) (**Figure 5**). Preoperative administration of pregabalin cut down postoperative opioid consumptions in the orthopedic surgeries and the thoracic and abdominal surgeries (SMD, -1.32, 95% CI: -2.22 to -0.42, SMD, -2.21, 95% CI: -2.98 to -1.44, respectively), but did not display such effect in the ENT or gynecological surgeries (SMD, -0.36, 95% CI: -0.87 to 0.15, SMD, -1.70, 95% CI: -4.06 to 0.66, respectively) (**Figure 6**, **Table 5**).

Side effects

Side effects were presented in **Table 6**. The side effects were limited to the first postoperative 24 hours. Studies indicated that pregabalin decreased the risk of PONV and nausea (RR, 0.60, 95% CI: 0.41 to 0.88, P=0.010, RR, 0.61, 95% CI: 0.38 to 0.99, P=0.044, respectively) while vomiting was not found to reach statistically different when evaluated alone. Combined

Table 4. Pain score at rest of different surgery type within 24 h

Outcome	No of studies	No of participants	Standardized mean difference (95% CI)	I-squared	Z	P
Thoracic and abdominal surgery	8 [60, 61, 63, 64, 67, 72-74]	456	-0.48 (-0.95 to -0.01)	80.6%	2.00	0.046
Orthopedic surgery	3 [66, 68, 71]	159	0.11 (-0.23 to 0.46)	17.1 %	0.64	0.524
ENT surgery	3 [62, 65, 70]	233	-0.91 (-1.60 to -0.23)	83.8%	2.62	0.009
Gynecological surgery	1 [69]	86	-0.18 (-0.24 to 0.61)	-	0.84	0.400

ENT, ophthalmology and otorhinolaryngology; CI, Confidence Interval.

Table 5. Opioid consumption of different surgery type within 24 h

Outcome	No of studies	No of participants	Standardized mean difference (95% CI)	I-squared	Z	P
Thoracic and abdominal surgery	7 [60, 61, 63, 64, 67, 73, 74]	402	-2.21 (-2.98 to -1.44)	89.4%	5.62	0.000
Orthopedic surgery	4 [66, 68, 71, 76]	219	-1.32 (-2.22 to -0.42)	88.6%	2.88	0.004
ENT surgery	1 [65]	60	-0.36 (-0.87 to 0.15)	-	1.37	0.171
Gynecological surgery	2 [69, 75]	146	-1.70 (-4.06 to 0.66)	96.80%	1.41	0.158

ENT, ophthalmology and otorhinolaryngology; CI, Confidence Interval.

Table 6. Side-effects within 0-24 h after pregabalin administration

Side-effect	number of study	RR (95% CI)	I^2 (%)	*P* value
Nausea	8 [1, 61-63, 65, 69, 71, 72]	0.61 (0.38, 0.99)	42.8	0.044*
Vomiting	6 [61-63, 65, 69, 71]	0.73 (0.30, 1.76)	29.0	0.478
PONV	6 [60, 64, 67, 70, 73, 75]	0.60 (0.41, 0.88)	45.8	0.010*
Sedation	3 [60, 71, 72]	2.11 (0.85, 5.24)	0.0	0.108
Headache	7 [1, 60, 61, 65, 69, 71, 73]	1.22 (0.78, 1.92)	0.0	0.382
Respiratory depression	4 [60, 61, 71, 73]	1.88 (0.31, 11.24)	0.0	0.489
Dizziness	9 [1, 61, 65, 67, 70-73, 75]	1.32 (0.80, 2.17)	26.2	0.275
Visual disturbance	6 [1, 61, 65, 67, 69, 73]	2.22 (0.90, 5.49)	15.7	0.085

Data are presented as RR (95% CI) (number of studies included in the analysis); PONV, postoperative nausea and vomiting.
*Indicates statistically significance (P≤0.05).

data showed no statistically significance in other adverse effects such as sedation (RR, 2.11, 95% CI: 0.85 to 5.24, P=0.108), dizziness (RR, 1.32, 95% CI: 0.80 to 2.17, P=0.275), headache (RR, 1.22, 95% CI: 0.78 to 1.92, P=0.382), respiratory depression (RR, 1.88, 95% CI: 0.31 to 11.24, P=0.489) or visual disturbance (RR, 2.22, 95% CI: 0.90 to 5.49, P=0.085).

Discussion

This meta-analysis of randomized controlled trails suggested that a single dose of preoperative administration of pregabalin could attenuate the acute postoperative pain though it may cause some adverse effects when compared with placebo.

Postoperative analgesia has gradually become the focus of clinical studies recently. In clinical practice, doctors implement multimodal postoperative analgesia, which can effectively prevent the occurrence of postoperative pain. Multimodal postoperative analgesia is mainly based on the combination of opioids, nonsteroidal anti-inflammatory drugs (NSAIDs) or paracetamol, small-dose ketamine, and perioperative administration of local anesthetics [77]. However, the application of opioid drugs may cause a series of side effects such as nausea, vomiting, sedation, pruritus and so on [78]. The use of NSAIDs is associated with gastrointestinal bleeding and renal toxicity. Recently, gabapentin has been used as an adjunct for managing acute postoperative pain. As a successor of gabapentin, many advanced clinical researches have focused on the efficacy of pregabalin in the treatment for acute postoperative pain. However, the results of clinical studies are conflicting and lack of definite conclusion, there

are no dosing guidelines for the use of pregabalin in the management of postoperative pain for the present.

This article analyzed the studies of preoperative single dose of pregabalin. Various doses of pregabalin diplayed different effects on the postoperative analgesia. Taking large heterogeneity into account, we used a random effect model and sensitivity analysis to analysis the source of heterogeneity. Within 24 h, 75 mg and 150 mg pregabalin did not exert analgesic effect and with the increase of dose to 300 mg, pain scores and opioid consumptions were significantly reduced. Since only three doses were included in this meta-analysis, the effect of other doses on acute postoperative pain was unclear.

In the previous clinical studies, the postoperative analgesic effect of pregabalin was supported in patients undergoing spinal fusion surgery [79], laparoscopic hysterectomy [20], dental surgery [80] and day-case gynecological laparoscopic surgery [19]. Depending on the parts of the operation, the studies, which included in this study were divided into four categories, namely the thoracic and abdominal surgery, ENT surgery, orthopedic surgery and gynecological surgery. Since the gynecological surgery was a special type of operations in abdomen, it was treated as a separate subgroup. The results showed that pregabalin not only decreased the postoperative pain scores but also saved the use of opioids in the thoracic and abdominal surgeries. Only 3 studies of ENT surgery were included in this meta-analysis, the outcomes were not illustrated about pregabalin for its postoperative analgesic effect. Pregabalin administration before gynecological surgery did not attenuate acute postoperative pain.

The adverse effects were extracted only in the first postoperative 24 h in our current meta-analysis. The data were pooled regardless of pregabalin dose. The incidence of PONV was reduced by 40% in pregabalin group compared to placebo group and that of nausea was reduced by 39%, but no statistically significance was suggested when vomiting was reported alone. In addition, there was no comparable difference among dizziness, headache, sedation, visual disturbance or respiratory depression between pregabalin and control group. Pregabalin administered preoperatively decreased postoperative pain scores, brought opioid-sparing effect and reduced the incidence of PONV and nausea, which were common opioid-related adverse effects. No patient was reported to withdraw because of adverse effects, suggesting pregabalin treatment was well tolerable.

As we know, heterogeneity is inevitable in a meta-analysis. In our Different pregabalin doses and surgery types in our analysis were combined, which could create heterogeneity within that analysis. As various anesthesia methods could influence the analgesic effect of pregabalin, so we just select the GA study. In addition, due to the different tolerance of patients for pain, the assessment of pain scores and opioid consumption showed a large amount of variations. It may be the main source of heterogeneity. The outcome of sensitive analysis is relatively stabilized.

This meta-analysis is about the prevention of postoperative pain using a preoperative single dose of pregabalin. Some limitations still exist. We do the subgroup analysis according to the pregabalin doses and the type of surgeries, but it cannot be unified by operative duration, the amount of narcotic drugs or anesthesitics. These might potentially influence the results and generate heterogeneity.

In conclusion, it is likely that preoperative pregabalin is beneficial for postoperative analgesia and diminishes the consumptions of opioids, but its effects range from pregabalin dose to surgery types. In addition, it leads to some side effects.

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Disclosure of conflict of interest

None.

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