

Effects of a single dose of preoperative pregabalin and gabapentin for acute postoperative pain: a network meta-analysis of randomized controlled trials

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Background: Pregabalin (PGB) and gabapentin (GBP) are current and emerging drugs in the field of pre-emptive preoperative analgesia. However, the role of PGB or GBP in acute postoperative pain management still remains elusive.

Materials and methods: We conducted a comprehensive literature search of articles published by December 3, 2017. A total of 79 randomized controlled trials with 6,201 patients receiving single-dose premedication were included. Through a network meta-analysis (NMA), we validated the analgesic effect and incidence of adverse events by using various doses of PGB or GBP administration.

Results: NMA results suggested that the analgesic effect may be dose related. For 24-hour opioid consumption, a consistent decrease was found with the increase in the dose of PGB or GBP. For 24-hour pain score at rest, a high dose (≥ 150 mg) of PGB was more effective in decreasing pain score than a dose of 75 mg, and a high dose (≥ 900 mg) of GBP reduced pain intensity than doses of 300 or 600 mg. Moreover, the incidence of adverse reactions varied with varying doses of PGB or GBP.

Conclusion: A dose–response relationship was detected in opioid consumption and postoperative pain for a single-dose preoperative administration of PGB and GBP. Making reasonable choice of drugs and dosage may prevent the occurrence of adverse reactions.

Keywords: PGB, GBP, single dose, acute postoperative pain, network meta-analysis

Introduction

Acute postoperative pain associated with surgical wounds is commonly encountered in most patients after a surgical procedure.¹ Additionally, improper postoperative pain management is significantly related to higher risk of occurrence of severe complications to patients, such as delayed trauma recovery, pulmonary embolism, as well as myocardial ischemia.^{2–4}

Since pre-emptive preoperative analgesia was first proposed by Wall in 1988, over the years it has been gradually regarded as an intervention given before incision, facilitating advance mobilization and functional rehabilitation after surgery.^{5–7} Pre-emptive analgesia focuses on reducing postoperative opioid consumption and pain levels, decreasing the incidence of adverse events and improving patient satisfaction. Several pre-emptive analgesic regimens have been tried in the perioperative period, including opioids, nonsteroidal anti-inflammatory drugs, and so on.^{8,9} Pregabalin

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(PGB) or gabapentin (GBP) is a current and emerging drug in this field. Although its use for the management of postoperative pain is off-label, its perioperative oral use has become widespread. So far, many meta-analyses have investigated the efficacy of perioperative PGB or GBP administration for preventing acute postoperative pain. However, the role of PGB or GBP in acute postoperative pain management still remains elusive. For instance, the study conducted by Jiang et al¹⁰ showed that PGB appeared to be efficacious in providing relief from postoperative pain, reducing analgesic consumption, and lowering the risk of nausea following spine surgery. Nevertheless, Eipe et al¹¹ demonstrated that the analgesic effectiveness of PGB was significantly limited to surgery associated with pronociceptive mechanisms. Additionally, previous studies were largely restricted to specific doses or methods of perioperative PGB or GBP administration.^{10,11} Consequently, in the present study, we aim to compare the analgesic effect and incidence of adverse events by administering different doses of PGB or GBP before surgery, and we expect to provide more insights into the optimal dose and drug selection of preemptive analgesics.

Materials and methods

Strategy and criteria of search

The following databases were searched: PubMed, Embase, and the Cochrane Library with the last update by December 3, 2017. The corresponding search term combinations were (“pregabalin” or “gabapentin”) AND (“pain” or “analgesia”) AND (“random*”). After excluding duplicate studies, we screened eligible studies manually by reviewing the titles, abstracts, and full papers.

Inclusion criteria: randomized clinical trials were included if they satisfied the following selection criteria: 1) premedication with single dose of PGB or GBP; 2) acute postoperative pain; and 3) operation under intravertebral anesthesia or general anesthesia.

Exclusion criteria: 1) multiple-dose oral administration of PGB and GBP (long-term preoperative administration or postoperative administration); 2) chronic postoperative pain; 3) operation under local anesthesia; 4) unable to extract any data; and 5) not published in English or Chinese.

Outcomes

Eight groups were set up by the dose treatments of PGB and GBP: placebo (PBO), PGB 75 mg, PGB 150 mg, PGB 300

mg, GBP 300 mg, GBP 600 mg, GBP 900 mg, and GBP 1,200 mg.

Primary outcomes (analgesic effect): 1) opioid consumption, 2) pain score at rest (visual analog scale or numeric rating scale score), and 3) pain score at movement. (All data were recorded within 24 hours after surgery.)

Secondary outcomes (adverse events): 1) PONV (postoperative nausea and vomiting within 24 hours after surgery); 2) nausea; 3) vomiting; and 4) dizziness.

Data extraction

The corresponding data were independently extracted from the selected studies by two independent investigators, and any controversies were resolved through consultation with the third reviewer. The following data were acquired from qualified studies and performed in Supplemental Digital Content: first author, published year, sample size, sex, type of surgery and anesthesia, PGB or GBP administration time, and clinical outcomes. The Cochrane Collaboration's Risk of Bias Tool was used for randomized controlled trials to estimate the quality assessment of the included study.¹²

Statistical analysis

A network meta-analysis (NMA) was conducted by integrating both direct and indirect evidence by using STATA software (version 14.0). We used PBO as a reference treatment in all analyses. Additionally, standardized mean difference (SMD) was used to estimate the outcomes (pain score at rest, pain score at movement, and opioid consumption) of the different doses of PGB and GBP. Moreover, OR was used to describe the outcomes of PONV, nausea, vomiting, and dizziness. Surface under the cumulative ranking curve (SUCRA) was conducted to represent the corresponding ranking of each outcome, and the higher the SUCRA values, the more preferable the intervention. After that, the assessment of the degree of inconsistency between direct and indirect evidence in each loop was conducted by using the node-splitting method. Also, risk of publication bias was indicated by funnel plots. Through sensitivity analyses, we considered opioid consumption as the most objective outcome, which was the most reported and had the largest heterogeneity variance. Our sensitivity analyses consisted of excluding studies that reported median instead of mean. The mean estimate was equal to the median, while SD approximates the quartile range, divided by 1.35 or the range divided by 4.

Results

Description of included studies

As Figure 1 illustrates, 4,785 records were retrieved from the PubMed, Embase, and Cochrane Library in the initial

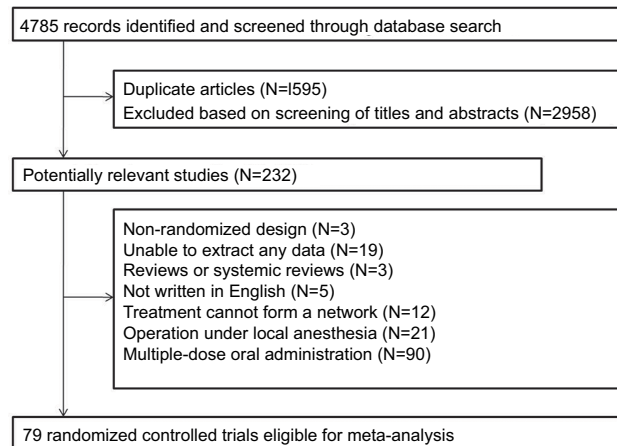


Figure 1 Flow chart of literature search and study selection, inclusion and exclusion.

literature search. After exclusion of duplicate articles and screening of titles and abstracts, 232 citations remained for further analysis. Finally, 79 randomized controlled trials with 6,201 patients were subject to full-text review.^{13–91} These studies were performed from 2002 to 2017 in 23 countries. Patients included in the studies underwent various types of surgeries: obstetrics and gynecology surgery (22.8%), spinal surgery (10.1%), orthopedic joint surgery (17.7%), urology surgery (7.6%), visceral surgery (16.4%), cardiac surgery (3.8%), and others (20.3%). Additionally, 62 studies (78.5%) used general anesthesia and the others (21.5%) used spinal anesthesia. The administration time varied between these studies: (29.1%) ≤ 1 hour before surgery, (41.8%) > 1 hour before surgery, (17.7%) ≤ 1 hour before anesthesia, and (10.1%) > 1 hour before anesthesia. One study did not provide details of the administration time (Table S1). The network of eligible comparisons is presented in Figure 2. In addition, 62 studies were two-arm trials (two of them were based on comparison between PGB and GBP), 13 were three-arm trials (three test samples were

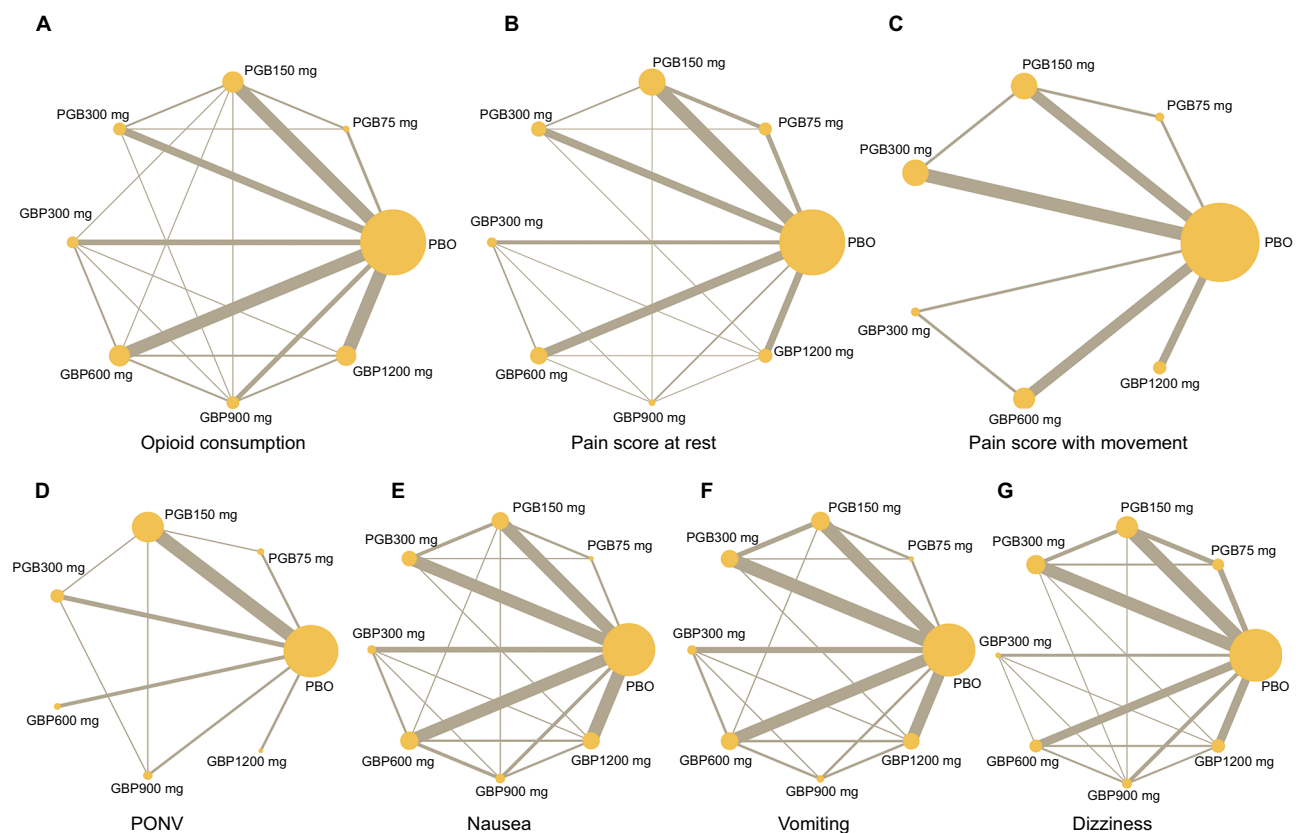


Figure 2 Network plots of eligible comparisons of all interventions including PBO, PGB 75 mg, PGB 150 mg, PGB 300 mg, GBP 300 mg, GBP 600 mg, GBP 900 mg, and GBP 1,200 mg.

Notes: (a) Network plots of opioid consumption. (b) Network plots of pain score at rest. (c) Network plots of pain score with movement. (d) Network plots of PONV. (e) Network plots of nausea. (f) Network plots of vomiting. (g) Network plots of dizziness. The size of each node is proportional to the number of sample size.

Abbreviations: GBP, gabapentin; PBO, placebo; PGB, pregabalin; PONV, postoperative nausea and vomiting within 24 hours after surgery.

involved: PGB, GBP, and PBO), two were four-arm trials, and one was five-arm trial.

Primary outcomes (analgesic effect)

Fifty-two studies, including a total of 3,827 patients, reported data for postoperative opioid consumption. All interventions consumed less opioids than PBO, and administration of increasing dose of PGB or GBP significantly decreased the consumption of opioids (Figure 3). The following results were obtained: PGB 150 mg vs PBO: SMD -1.66, 95% CI -2.28 to -1.03; PGB 300 mg vs PBO: SMD -1.86, 95% CI -2.68 to -1.03; GBP 300 mg vs PBO: SMD -0.98, 95% CI -1.86 to -0.10); GBP 600 mg vs PBO: SMD -1.14, 95% CI -1.77 to -0.50; GBP 900 mg vs PBO: SMD -1.64, 95% CI -2.60 to -0.67; GBP 1,200 mg vs PBO: SMD -1.86, 95% CI -2.51 to -1.21. No significant differences were found between the PGB 75 mg and control groups (PGB 75 mg vs PBO: SMD -0.18, 95% CI -1.46 to 1.09). SUCRA curve graph is shown in Figure 4. The four largest SUCRA values

for postoperative opioid consumption were as follows: GBP 1,200 mg (81.1), PGB 300 mg (80.1), PGB 150 mg (70.9), and GBP 900 mg (69.4).

Forty-eight studies, including a total of 3,664 patients, reported data for pain score at rest. Patients with PGB (150/300 mg) and GBP (900/1,200 mg) exhibited significantly less pain compared with those with PBO (Figure 3). The results were as follows: PGB 150 mg vs PBO: SMD -0.96, 95% CI -1.32 to -0.60; PGB 300 mg vs PBO: SMD -0.50, 95% CI -0.93 to -0.07; GBP 900 mg vs PBO: SMD -1.11, 95% CI -1.98 to -0.24; GBP 1,200 mg vs PBO: SMD -0.89, 95% CI -1.36 to -0.43, and no significant differences were found between patients taking others doses and PBO. The three largest SUCRA values for pain score at rest were as follows: GBP 900 mg (86.1), PGB 150 mg (83.6), and GBP 1,200 mg (77.6) (Figure 4).

Fifteen studies, including a total of 1,215 patients, reported data for pain score at movement. No significant differences were found between any of the interventions and control

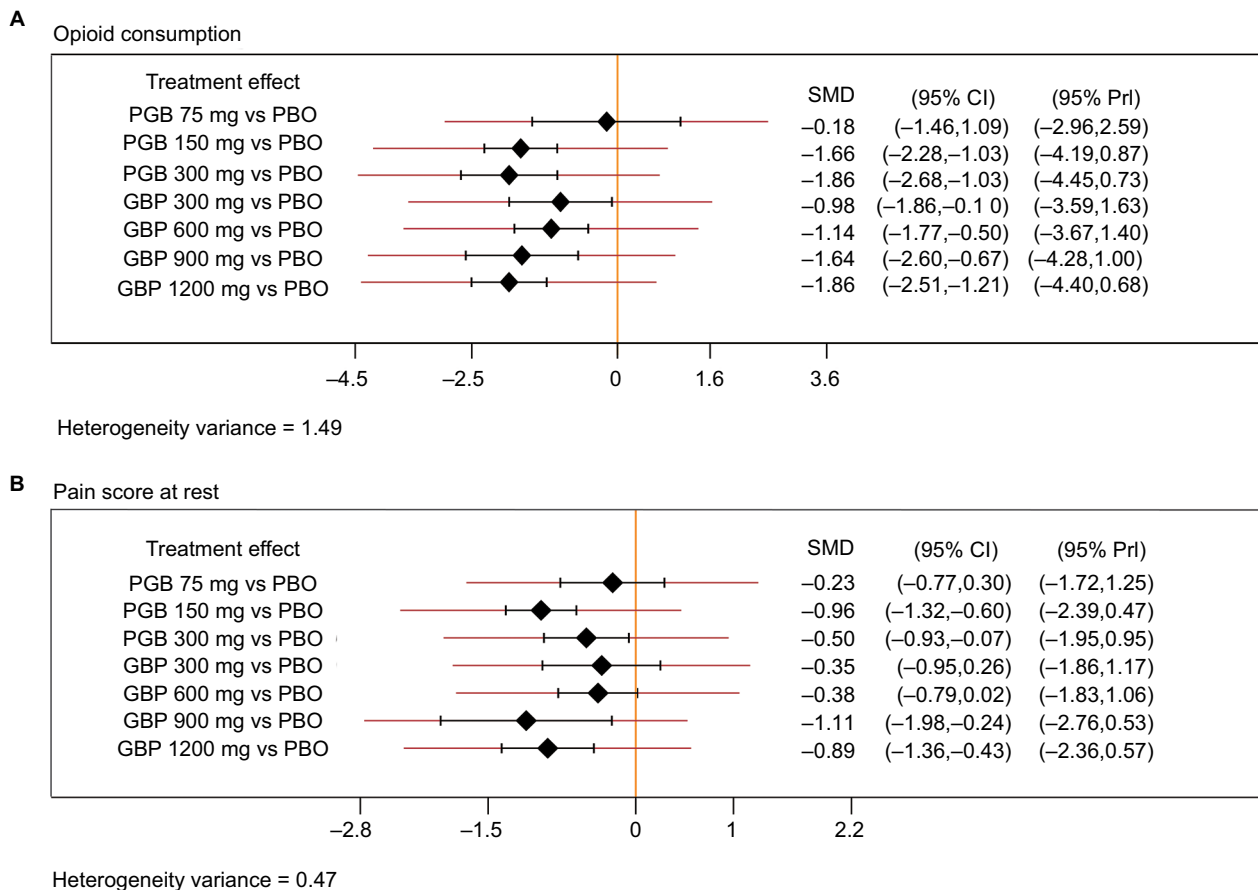


Figure 3 Forest plots of all interventions.

Notes: (a) Forest plots of the association between all interventions and opioid consumption. (b) Forest plots of the association between all interventions and pain score at rest. Patients with PGB (150/300 mg) and GBP (900/1,200 mg) exhibited significantly less pain compared with those with PBO.

Abbreviations: GBP, gabapentin; PBO, placebo; PGB, pregabalin; SMD, standardized mean difference.

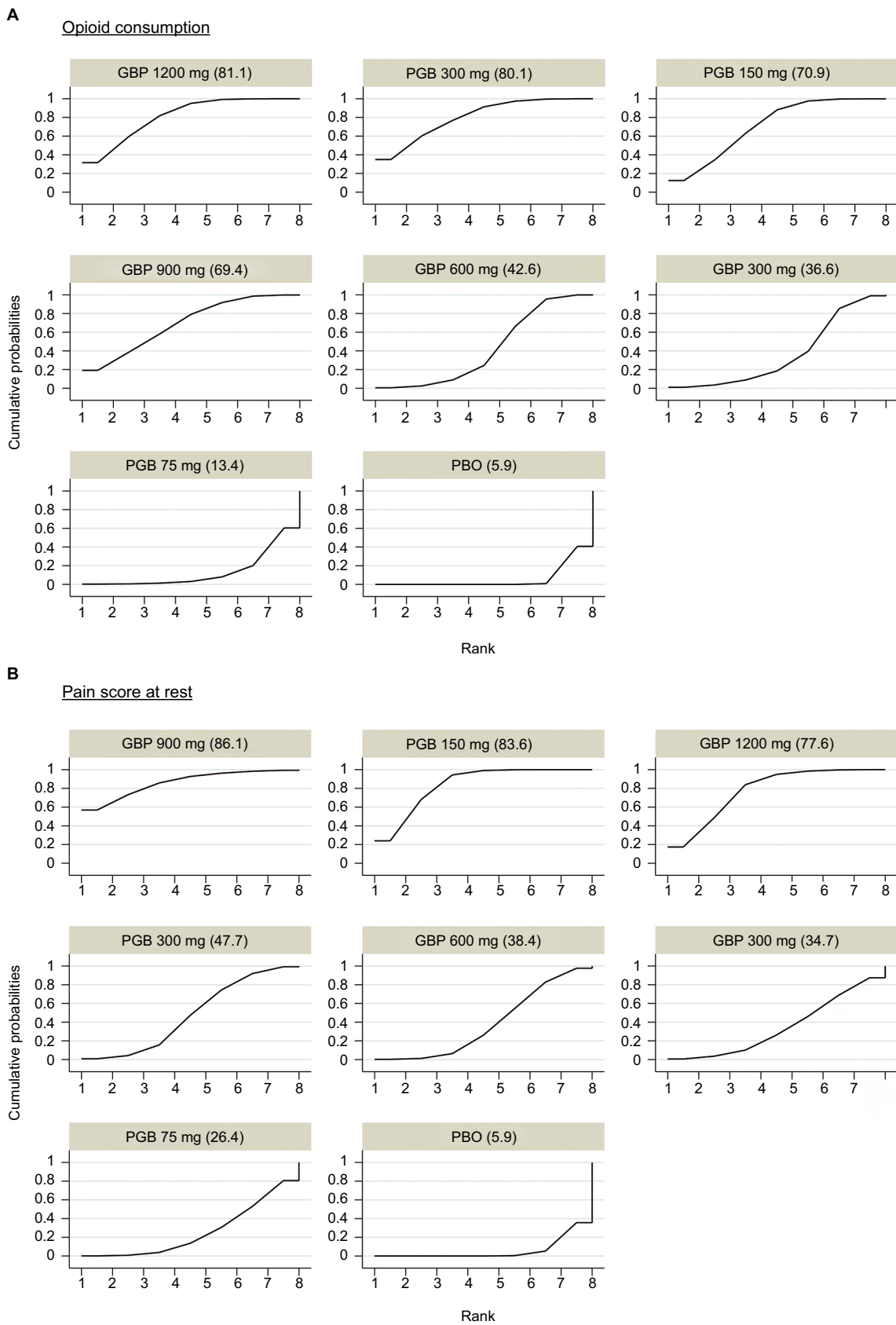


Figure 4 Ranking of SUCRA values.

Notes: (a) Ranking of SUCRA values of opioid consumption. (b) Ranking of SUCRA values of pain score at rest.

Abbreviations: GBP, gabapentin; PBO, placebo; PGB, pregabalin; SUCRA, surface under the cumulative ranking curve.

groups. Only the SUCRA values of GBP 1,200 mg (78.3) and PGB 150 mg (68.0) were larger than PBO (50.9) (Table 1).

Secondary outcomes (adverse events)

Overall, PGB 300 mg reduced the incidence of PONV (PGB 300 mg vs PBO: OR 0.18, 95% CI 0.09, 0.37) and nausea

(PGB 300 mg vs PBO: OR 0.50, 95% CI 0.35, 0.72) compared with the control groups. In addition, patients with GBP 1,200 mg showed higher incidence of PONV (GBP 1,200 mg vs PBO: OR 5.21, 95% CI 1.48, 18.34). However, incidence of dizziness increased when PGB 150 mg or PGB 300 mg was used (PGB 150 mg vs PBO: OR 1.94, 95% CI 1.10, 3.42;

Table 1 SUCRA value and effect size in comparison to PBO

Pain score with movement	Study	Patient	SUCRA	SMD	95% CI
GBP 1,200 mg	3	85	78.3	-0.4	(-1.25, 0.46)
PGB 150 mg	4	186	68.0	-0.22	(-0.91, 0.48)
PBO	15	542	50.9		
PGB 75 mg	1	45	47.8	0.03	(-1.26, 1.32)
GBP 300 mg	1	44	45.3	0.11	(-1.19, 1.40)
PGB 300 mg	5	183	44.2	0.07	(-0.56, 0.71)
GBP 600 mg	4	130	15.6	0.52	(-0.22, 1.26)
Total number of patients	1,215				
Incidence of PONV	Study	Patient	SUCRA	OR	95% CI
PGB 300 mg	4	119	97.1	0.18	(0.09, 0.37)
GBP 600 mg	3	141	80.4	0.32	(0.16, 0.65)
GBP 900 mg	2	60	53.1	0.59	(0.23, 1.53)
PGB 75 mg	2	80	52.5	0.6	(0.24, 1.50)
PGB 150 mg	11	384	44.1	0.74	(0.50, 1.09)
PBO	20	680	22.4		
GBP 1,200 mg	2	52	0.3	5.21	(1.48, 18.34)
Total number of patients	1,516				
Incidence of nausea	Study	Patient	SUCRA	OR	95% CI
PGB 300 mg	11	364	89.0	0.5	(0.35, 0.72)
GBP 300 mg	5	157	74.4	0.58	(0.33, 1.01)
GBP 1,200 mg	12	327	53.8	0.73	(0.48, 1.10)
GBP 600 mg	11	355	51.0	0.75	(0.53, 1.08)
GBP 900 mg	2	45	44.3	0.82	(0.31, 2.13)
PGB 75 mg	2	73	37.1	0.87	(0.41, 1.85)
PGB 150 mg	11	391	34.9	0.86	(0.59, 1.25)
PBO	41	1,323	15.4		
Total number of patients	3,035				
Incidence of vomiting	Study	Patient	SUCRA	OR	95% CI
GBP 900 mg	2	45	73.6	0.42	(0.08, 2.16)
GBP 1,200 mg	9	246	67.6	0.58	(0.34, 1.00)
PGB 75 mg	2	73	56.2	0.65	(0.27, 1.57)
PGB 300 mg	11	375	53.6	0.69	(0.44, 1.09)
GBP 600 mg	9	300	53.4	0.7	(0.41, 1.18)
GBP 300 mg	5	157	44.6	0.74	(0.34, 1.61)
PGB 150 mg	11	386	37.2	0.81	(0.51, 1.31)
PBO	37	1,214	13.9		
Total number of patients	2,796				
Incidence of dizziness	Study	Patient	SUCRA	OR	95% CI
GBP 600 mg	9	289	75.1	0.93	(0.44, 1.97)
PBO	41	1,342	72.8		
PGB 75 mg	6	210	69.8	1	(0.42, 2.39)
GBP 300 mg	3	78	55.0	1.18	(0.26, 5.37)
GBP 1,200 mg	9	244	47.8	1.38	(0.67, 2.82)
GBP 900 mg	4	105	43.4	1.53	(0.54, 4.33)
PGB 150 mg	14	512	25.3	1.94	(1.10, 3.42)
PGB 300 mg	13	425	10.8	2.49	(1.46, 4.23)
Total number of patients	3,205				

Abbreviations: GBP, gabapentin; PBO, placebo; PGB, pregabalin; SUCRA, surface under the cumulative ranking curve; SMD, standardized mean difference.

PGB 300 mg vs PBO: OR 2.49, 95% CI 1.46, 4.23). No significant differences were found between the interventions and control groups for incidence of vomiting (Table 1). Complete forest plots of summary effects are displayed in [Figure S1](#).

Risk of bias assessment

The risk of bias assessment is presented in Figure 5 as well as in [Table S2](#). The most common high risk of bias was selective reporting (16.5%), which principally resulted from the consideration of incomplete outcome data. As illustrated in [Figure S2](#), no risk of publication bias was found for any outcomes. A contribution plot showed the risk of bias of each direct or indirect comparison, which is shown in [Figure S3](#).

Sensitivity analyses

We conducted sensitivity analyses for opioid consumption by excluding studies only reporting median instead of mean (n=8). SUCRA ranking for overall treatment was not markedly affected: PGB 300 mg (83.6), GBP 1,200 mg (82.4), GBP 900 mg (63.6.), PGB 150 mg (61.2), PGB 75 mg (42.8), GBP 600 mg (34.8), GBP 300 mg (29.1), and PBO (2.5). Heterogeneity variance was 1.19 ([Figure S4](#)).

Inconsistency

Node-splitting method was used to assess inconsistency in the analysis. Only a few loops had inconsistent results for each outcome ([Figure S5](#)).

Discussion

Pre-emptive analgesia given before incision focuses on managing postoperative pain including decreasing the consumption of analgesics as well as conferring neuroprotective characteristics.⁹ Although many meta-analyses have investigated the analgesic efficacy of perioperative PGB or GBP administration so far, the role of PGB or GBP in acute post-

operative pain management still remains elusive. Moreover, few studies compared different doses of abovementioned drugs for preventing acute postoperative pain.

Recently, the study performed by Fabritius et al⁹² demonstrated that they could not confirm a distinct relationship between the dose of GBP and the consumption of opioids, dividing all treatments into subgroups despite single or multiple doses, preoperative or postoperative administrations. In the present study, we presented an NMA to validate the effect of analgesic and risk of adverse events by a series of doses of PGB or GBP administration. Interestingly, our results indicated that a dose–response relationship was detected in analgesic effect of preoperative PGB or GBP treatment. For 24-hour opioid consumption, as an objective marker for measurements of pain relief in postoperative studies, a consistent decrease was found with the increase in the dose of GBP or PGB. For 24-hour pain score at rest, a high dose (≥ 150 mg) of PGB was more effective in decreasing pain score than dose of 75 mg, and a high dose (≥ 900 mg) of GBP reduced pain intensity than doses of 300 or 600 mg.

Recent paper suggested that PGB and GBP may share a similar mechanism in the treatment and prevention of postoperative pain, affecting one type of calcium channel to decrease the release of some neurotransmitters such as noradrenaline.^{93–95} Additionally, a nonlinear process of saturable absorption exists in orally administered GBP, making its plasma concentrations less predictable. In contrast, total bioavailability of PGB remains at more than 90% regardless of dose.^{96,97} A trial displayed by Ifuku et al⁹⁸ suggested that effectiveness of PGB on neuropathic pain was six times that of GBP.

Previous studies have disclosed that unalleviated postoperative pain was associated with various complications such as deep veins thrombosis, increased heart rate, and blood pressure.^{88,95} Our analysis also indicated that preoperative single-dose administration of PGB or GBP would influence the incidence of postoperative adverse reactions. Previously, Kohli et al⁸⁸ reported that the reduction of postoperative blood pressure, heart rate, as well as anxiety level was significantly related to preoperative single-dose administration of PGB. In the current study, of note, using a high dose (≥ 300 mg) of PGB preoperatively is one of the approaches to prevent PONV and nausea, but not vomiting. The underlying mechanism of preventing PONV and nausea by PGB may be as follows: 1) nausea and vomiting are one of the side effects of opioids; pre-emptive analgesia using PGB may reduce preoperative and intraoperative opioid requirements, thereby resulting in decreased incidence of PONV and nausea. 2) The

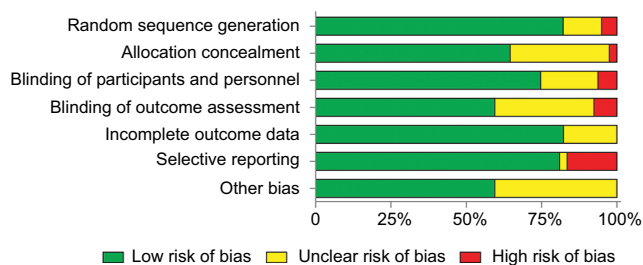


Figure 5 Risk of bias assessment.

Note: The most common high risk of bias was selective reporting (16.5%), which principally resulted from the consideration of incomplete outcome data.

reduction in tachykinin neurotransmission, calcium influx, as well as inflammatory response at the surgical site may explain the underlying mechanisms of anti-emetic properties of PGB.^{99,100}

A previous meta-analysis which investigated nausea and vomiting as the primary outcomes (44 studies, n=3,489) found that GBP is associated with a reduction in postoperative nausea and vomiting.¹⁰¹ However, there was no significant difference between control groups and GBP in our NMA. Recent findings have established that pharmacokinetic properties vary by PGB and GBP, which might be one of the reasons for the difference in our study. Orally administered GBP achieved maximum plasma concentrations within 3–4 hours, while PGB is absorbed more rapidly and attained the maximum plasma concentrations within 1 hour.⁹⁶ In addition, since we did not search for adverse effects alone in the database, the results in our study may be incomplete.

Highlights

Our NMA is the first dose-related NMA of the impact of PGB and GBP on acute postoperative pain, revealing that a suitable single dose of preoperative PGB or GBP administration has a significant effect in reducing opioid consumption and postoperative pain. In addition, our study comprehensively analyzed the analgesic effect combined with incidence of adverse events. The results suggested that a high dose (≥ 150 mg) of PGB can increase the rate of dizziness, and a high dose (≥ 300 mg) of PGB decreases the incidence of PONV and nausea, while GBP 1,200 mg increases the rate of PONV.

Limitations

First, the heterogeneity of opioid consumption could not be absolutely explained. In the current study, sensitivity analysis based on the type of data was focused on explaining it, but the analgesic effect of PGB or GBP may be confounded by patient characteristic, ethnic status, timing of administration, type of surgery, or intraoperative medication. Therefore, further data analysis is essential to avoid these interference factors. Second, we only included end points about opioid consumption and pain score with follow-up at 24 hours postoperatively. Third, the relatively small sample size of the certain included studies may have affected the accuracy of the effect size estimation.

Conclusion

The results of our current study demonstrated that a dose-response relationship was detected in opioid consumption and postoperative pain for a single-dose preoperative administration of PGB and GBP. Making reasonable

choice of drugs and dosage may prevent the occurrence of adverse reactions. Future clinical trials are required to determine the differences in analgesic effect between single-dose oral administration and multiple-dose oral administration. Furthermore, the optimal doses of these medications and timing of administration of pre-emptive analgesia still require further study, which may help make the standardization and rationalization of multimodal analgesia possible.

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Disclosure

The authors report no conflicts of interest in this work.

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