Randomized Trial

The Efficacy of Preoperative Gabapentin in Spinal Surgery: A Meta-Analysis of Randomized Controlled Trials

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Background: Pain management after spinal surgery has been studied for years. Gabapentin is a third-generation antiepileptic drug that selectively affects the nociceptive process and has been used for pain relief after surgery. However, the relationship between gabapentin and postoperative pain in spinal surgery is still controversial.

Objective: To assess the efficacy of the pre-emptive use of gabapentin in spinal surgery.

Study Design: A meta-analysis of randomized controlled studies.

Setting: The MEDLINE, EMBASE, ClinicalTrials.gov, and Web of Science databases were systematically searched.

Methods: This meta-analysis of randomized controlled trials (RCTs) was performed to compare the use of gabapentin with placebo in spinal surgery regarding to the following: the mean difference (MD) of postoperative opioid requirements, the changes of visual analog scale (VAS) scores in 2 groups, and the incidence rate of adverse effects. An electronic-based search of all related literatures was conducted, and only RCTs for spinal surgery were included. The MD of postoperative opioid requirements and VAS scores and the relative risk (RR) of the incidence rate of adverse effects in the gabapentin group versus the placebo group were extracted throughout the study.

Results: Ten trials, involving 827 patients, met the inclusion criteria and were included in this meta-analysis. The total morphine consumption was significantly lower over the first 24 hours postoperatively in the gabapentin group ($P < 0.05$). The VAS scores at 2, 4, 6, 12, and 24 hours were less in the gabapentin group ($P < 0.05$). The incidence rate of vomiting, pruritus, and urinary retention was significantly less in the gabapentin groups (RR = 0.53, 95% CI 0.32–0.86, $P < 0.05$; RR = 0.38, 95% CI 0.22–0.66, $P < 0.05$; RR = 0.57, 95% CI 0.34–0.98, $P < 0.05$, respectively).

Limitations: All of the studies we screened were published online except for unpublished articles. Only 10 RCTs met our inclusion criteria, so the sample size was still relatively small.

Conclusion: This meta-analysis suggests that the administration of gabapentin is effective in reducing postoperative opioid consumption, VAS scores, and some side effects after spinal surgery.

Key words: Gabapentin, analgesia, spinal surgery, meta-analysis, randomized controlled trials, visual analog scale score, side effect

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Spinal surgery is a common operation in modern medicine, but it is often associated with postoperative pain as well as large surgical incisions and relatively long operation times (1). The improvement of surgical techniques and perioperative period management might be a good way to relieve the pain, but the majority of patients undergoing spinal surgery still experience

intense pain after the operation. Poor control of postoperative pain may have negative effects on the cardiovascular and cerebrovascular systems and further affect the final operation outcomes (2). Under such circumstances, how to relieve the postoperative pain is an urgent issue for many doctors and the pre-emptive analgesia might be a feasible approach for clinical practice (3).

The pain management in spinal surgery is frequently directed at the reduction of the patient's pain score and narcotic requirement as well as adverse effects by multimodal analgesia techniques (4). Even if the multimodal analgesia method has been applied in clinic, postoperative pain may also occur in many patients (5,6). Considering the various adverse effects of opioid analgesics, the use of some non-opioid agents, such as gabapentin, is often recommended (7). As a third-generation anticonvulsant agent, gabapentin can selectively affect the nociceptive process by inhibiting calcium influx via voltage-gated calcium channels (8). It not only plays the key role in both central and peripheral analgesia, but it is also relatively well-tolerated (9).

There are various gabapentin formulations that are available in clinics and hospitals, which are frequently used in the management of chronic pain. Some of these include Gralise (extended-release gabapentin), Horizant (gabapentin enacarbil), and Lyrica (pregabalin). Although they have different pharmacokinetic properties, it is evident that these different formulations provide many clinical and therapeutic advantages owning to higher levels of drug tolerability and enhanced safety profiles (10,11). In past decades, some studies were conducted to evaluate the effects of pre-emptive gabapentin before the operation (12-15). Although some conclusions have been made, a rare meta-analysis was made for the assessment of pre-emptive use of gabapentin alone in spinal surgery. Trying to reveal the effect of gabapentin in the reduction of opioid consumption and visual analog scale (VAS) scores from randomized controlled trials (RCTs) is our major purpose. Further explorations of the adverse effects of gabapentin are discussed as well.

Methods

This meta-analysis followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (16). Since this is a meta-analysis of formerly published literatures, ethical approval was not required. All of the literatures were identified from different electronic-based searches, including MEDLINE, EMBASE, ClinicalTrials.gov, and Web of Science. The following keywords, combined with MeSH terms and their combinations, were used to maximize the search accuracy: "pain management, postoperative pain, spinal surgery, spinal fusion, interbody fusion, laminectomy, and gabapentin." Only RCTs in humans were included for this study. A PRISMA flow diagram can be viewed in Fig. 1.

Selection Criteria

Literatures were included if they met the following criteria:

- Types of studies: published in the English language
- Types of interventions: gabapentin and placebo
- Types of outcomes: at least one of the following items was reported: the cumulative consumption of morphine at 24 hours, the pain assessment score, or the incidence of adverse effects.

Two authors evaluated all of the eligible literatures independently and any disagreements between them were solved by discussion; if no consensus was made, the third author made the final decision as the adjudicator. The risk of bias was assessed according to the Cochrane Collaboration's tool, and the quality of the RCTs was evaluated by funnel plots (17).

Data Extraction

The following data were extracted and analyzed: the first author's name, the publication year, the number of patients, the type of spinal surgery, the gabapentin regimen and dose, the types and methods of opioids, the pain assessment methods, and the adverse reactions.

Statistical Analysis

The pooled data were analyzed with the use of RevMan 5.3 (The Nordic Cochrane Centre for The Cochrane Collaboration, Copenhagen, Denmark) and Stata 14 (StataCorp LP, College Station, TX). By the usage of chi-square tests, heterogeneity was evaluated by the value of I^2 and P; $I^2 < 50\%$ and $P = 0.1$ was considered as no substantial heterogeneity. Regarding to the continuous variables, the mean difference (MD) and 95% confidence intervals (CIs) were pooled to express the results. Relative risk (RR) and 95% CIs were calculated for dichotomous variables. $P < 0.05$ was considered statistically significant.

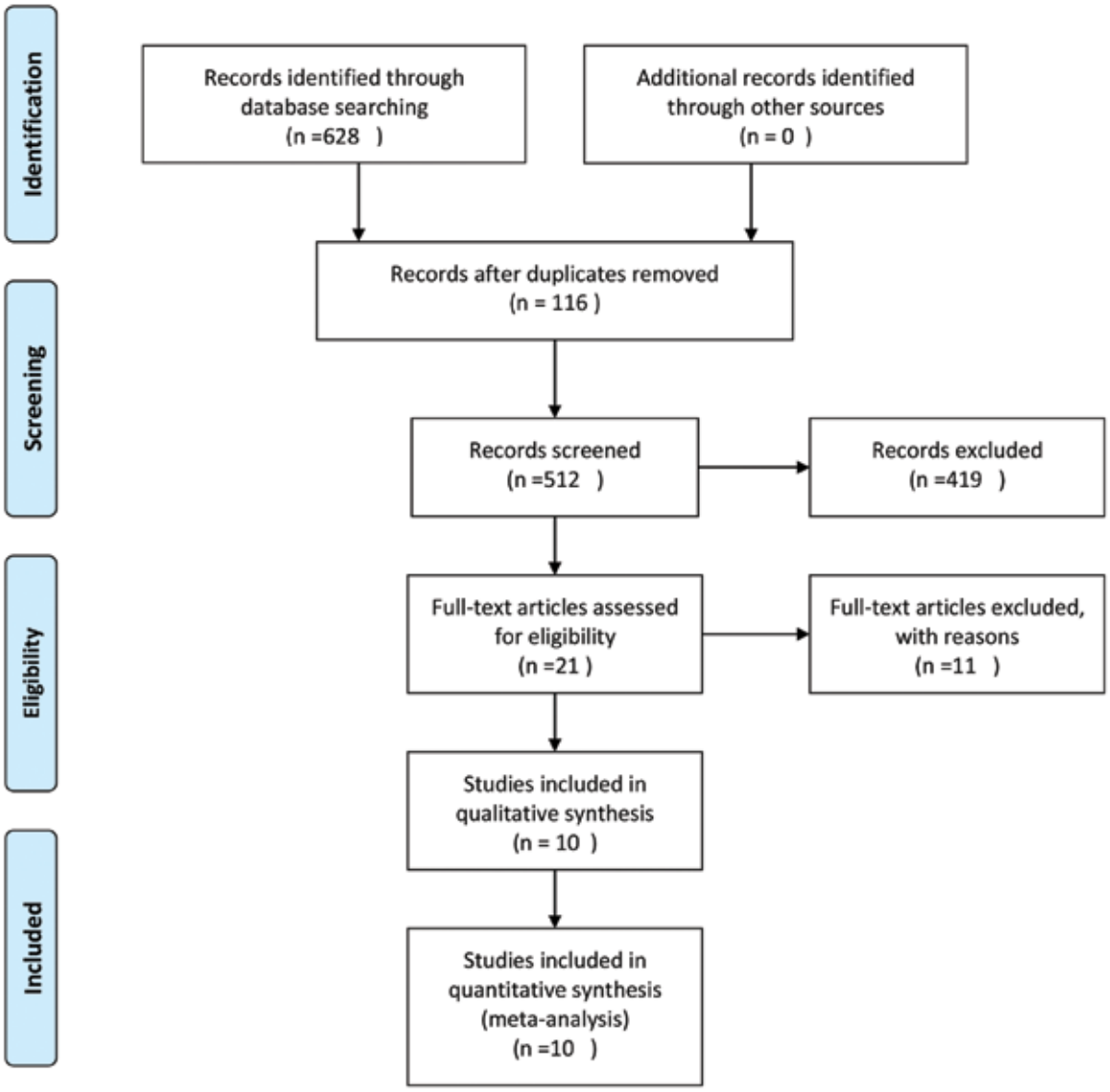

Fig. 1. *The selection of literature for the included studies.*

Results

Literature Search

A total of 628 potential records were identified with the electronic-based search, including 116 duplicated articles. After the primary screening, 491 irrelevant literatures were ruled out, leaving 10 RCTs to eventually fulfill the selection criteria (18-27). A total of 827 patients were included, and the research time interval was between 2004 and 2016. In 2 trials, gabapentin was administered preoperatively and postoperatively (24,27), whereas in the other 8 trials, gabapentin was given preoperatively only (18-23,25,26). In all of the pooled literatures, "Erten (900 mg) 2010" and "Erten (1200 mg) 2010" were the same trial, thus

Table 1. *The characteristics of the included studies.*

Clinical Trials	Age (yrs)	Gender (M/F)	Location	No. of Patients Gabapentin/Control	Dose of Gabapentin	Time of Gabapentin Administration
Erten (900 mg) 2010	44.2	21/19	Turkey	20/20	900 mg	1 h preoperatively
Erten (1200 mg) 2010	44.9	20/19	Turkey	19/20	1200 mg	1 h preoperatively
Khan (600 mg) 2011	42.3	31/19	Iran	25/25	600 mg	2 h preoperatively
Khan (900 mg) 2011	41.5	30/20	Iran	25/25	900 mg	2 h preoperatively
Khan (1200 mg) 2011	40.7	31/19	Iran	25/25	1200 mg	2 h preoperatively
Khurana 2014	48.1	44/16	India	30/30	300 mg	1 h preoperatively
Ozgencil2011	49.6	28/32	Turkey	30/30	600 mg	2 h preoperatively
Pandey 2004	38.8	38/18	India	28/28	300 mg	2 h preoperatively
Pandey (300 mg) 2005	39.8	28/12	India	20/20	300 mg	2 h preoperatively
Pandey (600 mg) 2005	40.2	27/13	India	20/20	600 mg	2 h preoperatively
Pandey (900 mg) 2005	41.6	23/17	India	20/20	900 mg	2 h preoperatively
Pandey (1200 mg) 2005	41.0	25/15	India	20/20	1200 mg	2 h preoperatively
Radhakrishnan 2005	40.7	40/20	India	30/30	800 mg	400 mg on the night before surgery + 400 mg 2 h preoperatively
Turan 2004	46.5	28/22	Turkey	25/25	1200 mg	1 h preoperatively
Vahedi 2011	44.4	44/32	Iran	36/40	300 mg	2 h preoperatively
Vasign 2016	49.6	59/17	Iran	38/38	900 mg	600 mg 2 h preoperatively + 300 mg 6 h postoperatively

we divided this trial into 2 different dose comparisons (900mg gabapentin vs. placebo and 1200 mg gabapentin vs. placebo). "Khan (600 mg) 2011", "Khan (900 mg) 2011", and "Khan (1200 mg) 2011" also belonged to one study, therefore, we divided this study into 3 different dose comparisons (600 mg gabapentin vs. placebo, 900mg gabapentin vs. placebo, and 1200 mg gabapentin vs. placebo). "Pandey (300 mg) 2005", "Pandey (600 mg) 2005", "Pandey (900 mg) 2005", and "Pandey (1200 mg) 2005" were the same trial as well; in order to investigate the influence of the dose, this trial was divided into 4 different comparisons (300 mg gabapentin vs. placebo, 600 mg gabapentin vs. placebo, 900 mg gabapentin vs. placebo, and 1200 mg gabapentin vs. placebo).

Study Characteristics

The key characteristics of the included gabapentin studies are illustrated in Table 1. All of the relevant literatures were small sample sizes, ranging from 19–38 patients. The statistically significant characteristics were extracted from 2 groups.

Risk of Bias Assessment

The Cochrane Collaboration's tool was used to evaluate the risk of bias in all of the included RCTs. The quality assessment of methodology is shown in Fig. 2. No high risk of bias was found in all of the included studies.

Outcomes of Intervention

Cumulative Consumption of Morphine at 24 Hours

300 mg of Gabapentin

Three trials reported the details of postoperative cumulative consumption of morphine under the usage of 300 mg gabapentin (22,23,26). The pooled results from the meta-analysis showed a positive effect of gabapentin in trials (MD = -1.74, 95% CI: -2.55 to -0.93, $P < 0.00$). No significant heterogeneity was found in the included studies ($\chi^2 = 3.15$, df = 2, $I^2 = 36\%$, $P = 0.21$; Fig. 3).

600 mg of Gabapentin

Three trials reported the details of postoperative cumulative consumption of morphine under the usage of 600 mg gabapentin (19,21,22). Compared with the placebo, gabapentin could significantly reduce the postoperative consumption of morphine (MD = -5.36,

95% CI: -6.27 to -4.45, P < 0.00). No significant heterogeneity was found in all of the included studies (χ^2 = 1.41, df = 2, I^2 = 0%, *P* = 0.49; Fig. 3).

900 mg of Gabapentin

Four trials reported the details of postoperative cumulative consumption of morphine under the usage of 900 mg gabapentin (18,19,22,27). Compared with the placebo, gabapentin showed a positive effect in the reduction of postoperative consumption of morphine (MD = -11.41, 95% CI: -19.75 to -3.08, P < 0.00). However, significant heterogeneity was found in the included studies (χ^2 = 195.05, df = 3, I^2 = 98%, P < 0.00; Fig. 3).

1200 mg of Gabapentin

Four trials reported the details of postoperative cumulative consumption of morphine under the usage of 1200 mg gabapentin (18,19,22,25). The pooled results from the meta-analysis showed a positive effect of gabapentin in trials (MD = -17.84, 95% CI: -28.20 to -7.47, P < 0.00). However, significant heterogeneity was also found in the included studies (χ^2 = 71.03, df = 3, I^2 = 96%, P < 0.00; Fig. 3).

Postoperative VAS Score at 2 Hours

Details regarding the postoperative VAS scores at 2 hours were available in 5 trials (18,21,24,27). Significant heterogeneity was found (χ^2 = 44.98, df = 4, I^2 = 91%, P < 0.00); therefore, a random-effects model was performed. Compared with the placebo, gabapentin could significantly reduce the postoperative VAS score at 2 hours (MD = -15.16, 95% CI: -23.75 to -6.58, *P* <0.00; Fig. 4).

Postoperative VAS Score at 4 Hours

Details regarding postoperative VAS scores at 4 hours were available in 4 trials (18,19,21,24,27). Significant heterogeneity was found (χ^2 = 123.07, df = 7, I^2 = 94%, *P* < 0.00); then, the random-effects model was performed. The result revealed a positive effect of gabapentin on the reduction of postoperative VAS scores at 4 hours (MD = -15.96, 95% CI: -24.47 to -7.44, *P* = 0.0002; Fig. 5).

Postoperative VAS Score at 6 Hours

Eleven trials reported VAS scores at 6 hours (18,19,21-24,27). Significant heterogeneity exists (χ^2 = 137.18, df = 10, I^2 = 93%, *P* < 0.00); therefore, a random-effects model was performed. Compared with the placebo, gabapentin could reduce the VAS score at 6 hours significantly (MD = -14.32, 95% CI: -20.79 to -7.85, *P* < 0.00; Fig. 6).

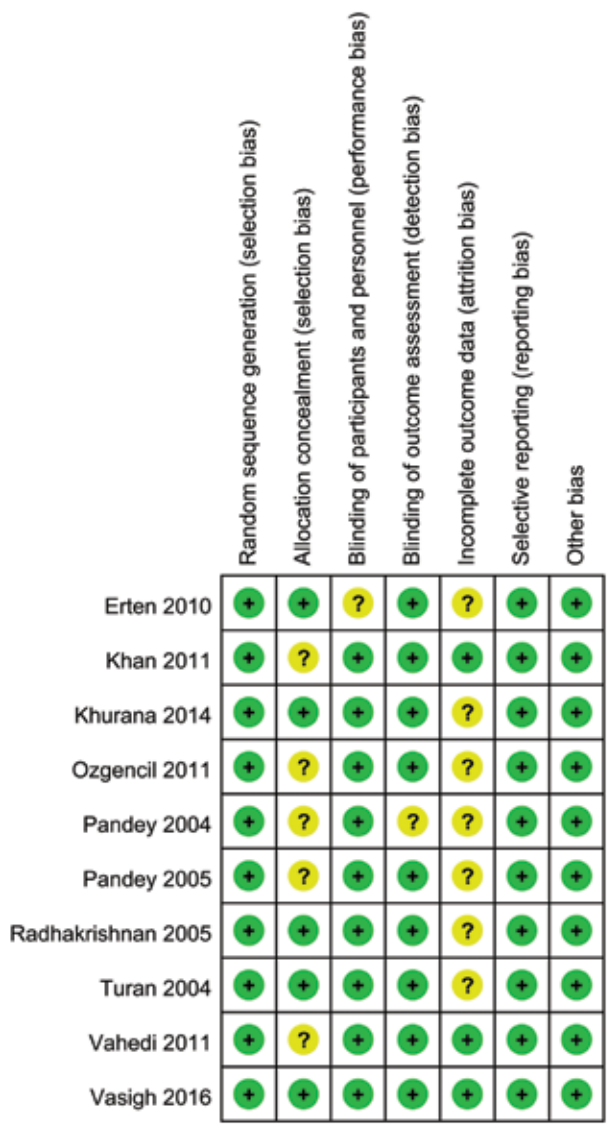

Fig. 2. *The summary of bias risk of RCTs.*

Postoperative VAS Score at 12 Hours

Details regarding the postoperative VAS at 12 hours were available in 6 trials (18,19,21-24,26,27). Significant heterogeneity was found; therefore, a random-effects model was used (χ^2 = 87.01, df = 12, I^2 = 0%, *P* < 0.00). The

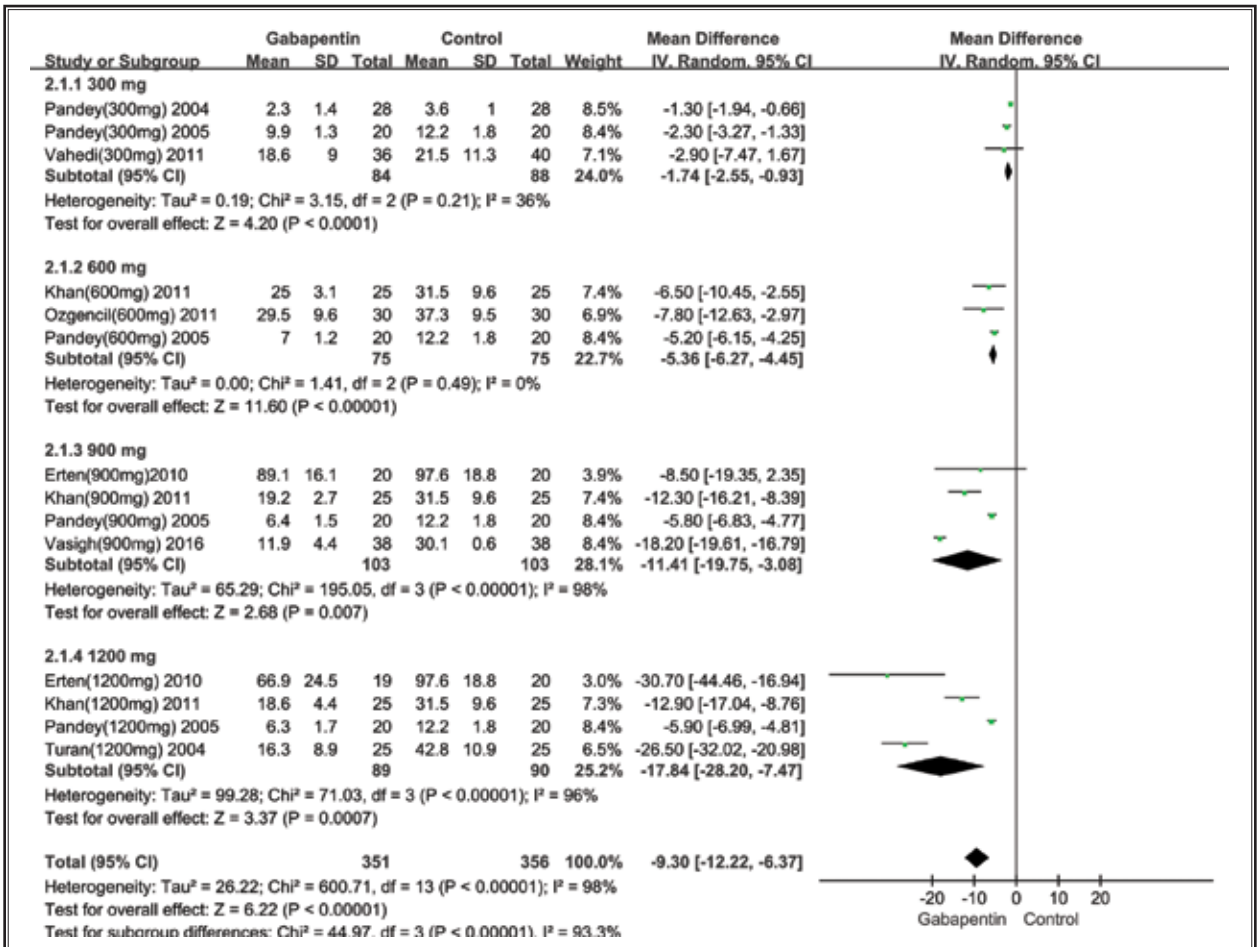

Fig. 3. *A forest plot of the postoperative opioid consumption at 24 hours between the 2 groups.*

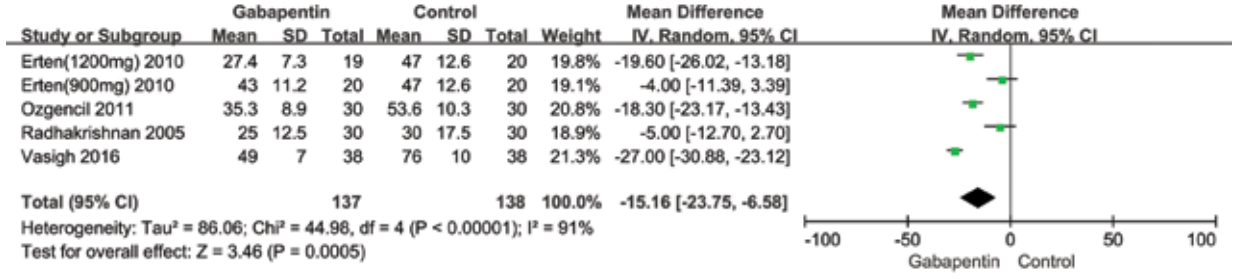

Fig. 4. *A forest plot of the postoperative VAS scores at 2 hours between the 2 groups.*

overall pooled results from the meta-analysis showed that gabapentin is quite effective in reducing the VAS score at 12 hours (MD = -11.64, 95% CI: -15.76 to -7.53, $P < 0.00$; Fig. 7).

Postoperative VAS Score at 24 Hours

This outcome was reported in 11 trials (18,19,21-24,26,27). Significant heterogeneity exists ($\chi^2 = 57.47$, df = 12, $I^2 = 79\%$, $P < 0.00$); then, a random-effects

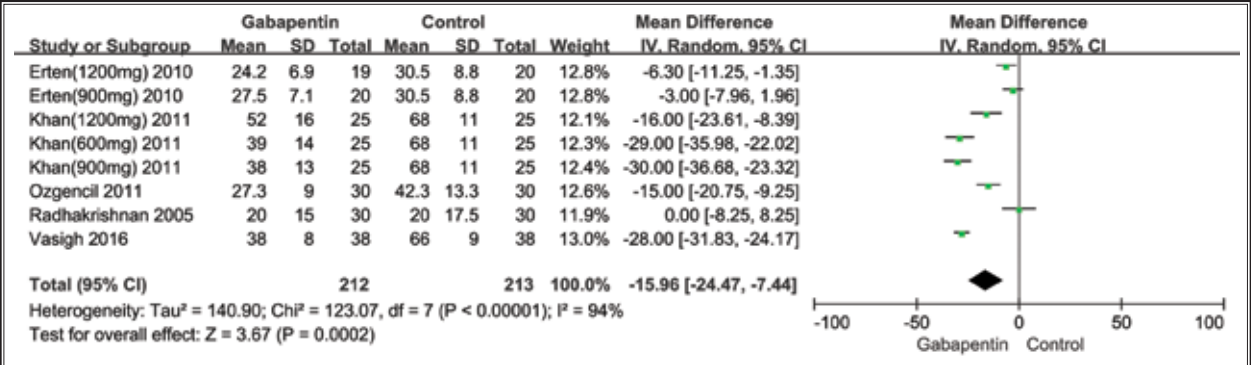

Fig. 5. *A forest plot of the postoperative VAS scores at 4 hours between the 2 groups.*

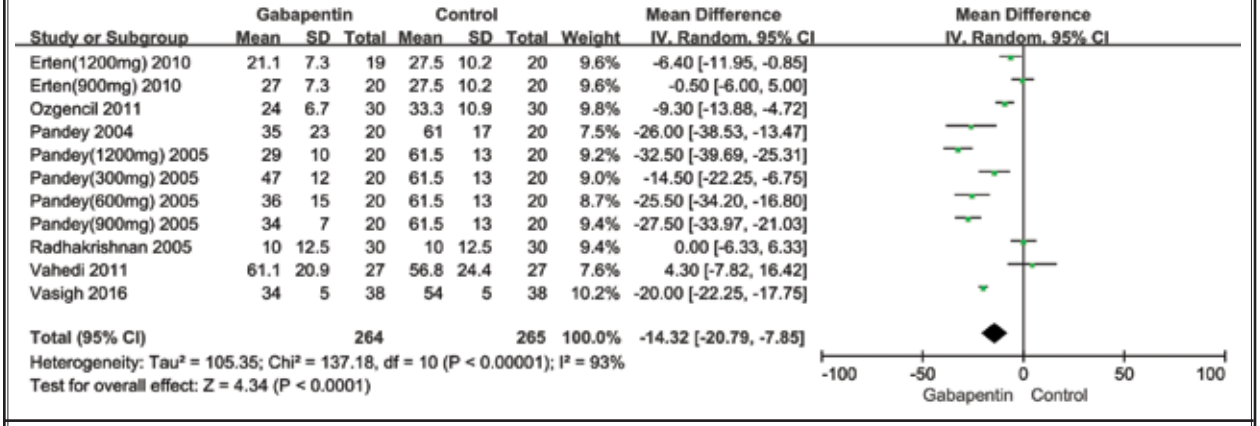

Fig. 6. *A forest plot of the postoperative VAS scores at 6 hours between the 2 groups.*

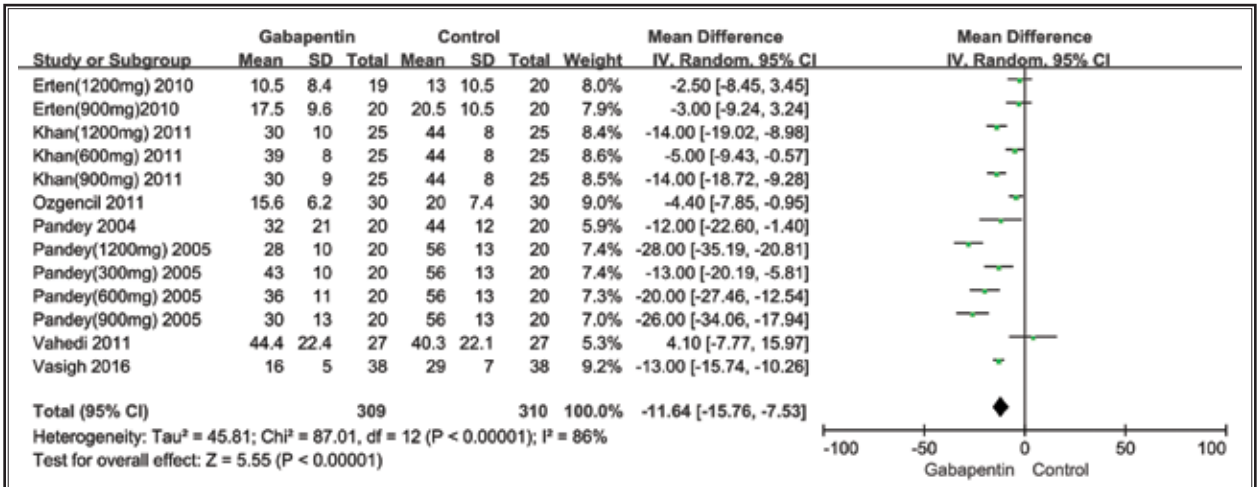

Fig. 7. *A forest plot of the postoperative VAS scores at 12 hours between the 2 groups.*

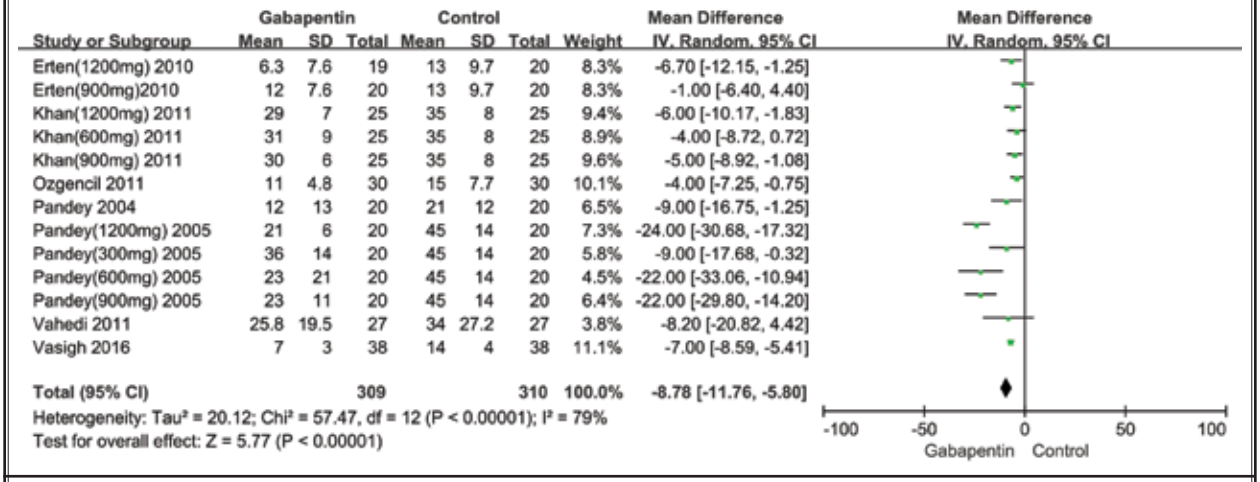

Fig. 8. *A forest plot of the postoperative VAS scores at 24 hours between the 2 groups.*

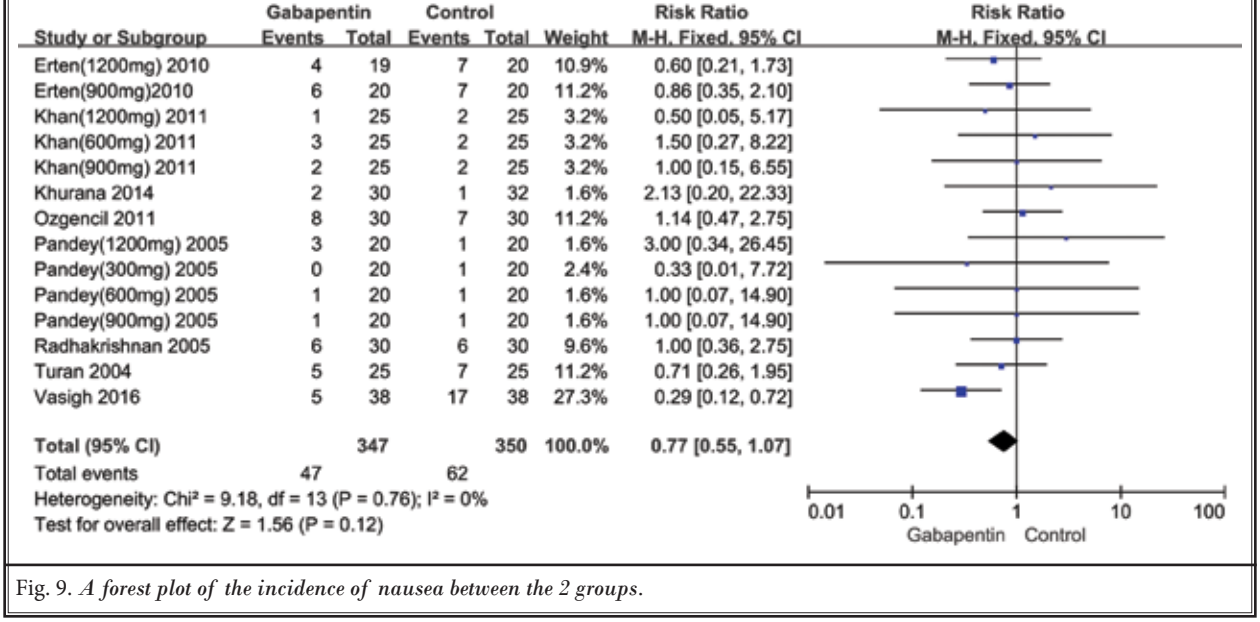

Fig. 9. *A forest plot of the incidence of nausea between the 2 groups.*

model was performed. Compared with the placebo, gabapentin could reduce the postoperative VAS score at 24 hours significantly (MD = -8.78, 95% CI: -11.76 to -5.80, $P < 0.00$; Fig. 8).

Adverse Effects

Nausea was the most common adverse effect in the included trials (18-22,24,25,27). Significant heterogeneity was not found in the included studies; therefore, a fixed-effects model was used ($\chi^2 = 9.18$, df = 13, $I^2 = 0\%$, $P = 0.76$). Compared with the placebo group, no positive result was found in the gabapentin group (RR = 0.77, 95% CI 0.55–1.07, $P = 0.12$; Fig. 9).

The second most reported side effect was vomiting and 12 studies analyzed the incidence rate of vomiting (19-22,24,25,27). No significant heterogeneity was found; therefore, a fixed-effects model was used ($\chi^2 = 6.14$, df = 11, $I^2 = 0\%$, $P = 0.86$). Compared with the placebo group, the incidence rate of vomiting was less in the gabapentin group (RR = 0.53, 95% CI 0.32–0.86, $P = 0.01$; Fig. 10).

The incidence of headache was reported by 7 trials

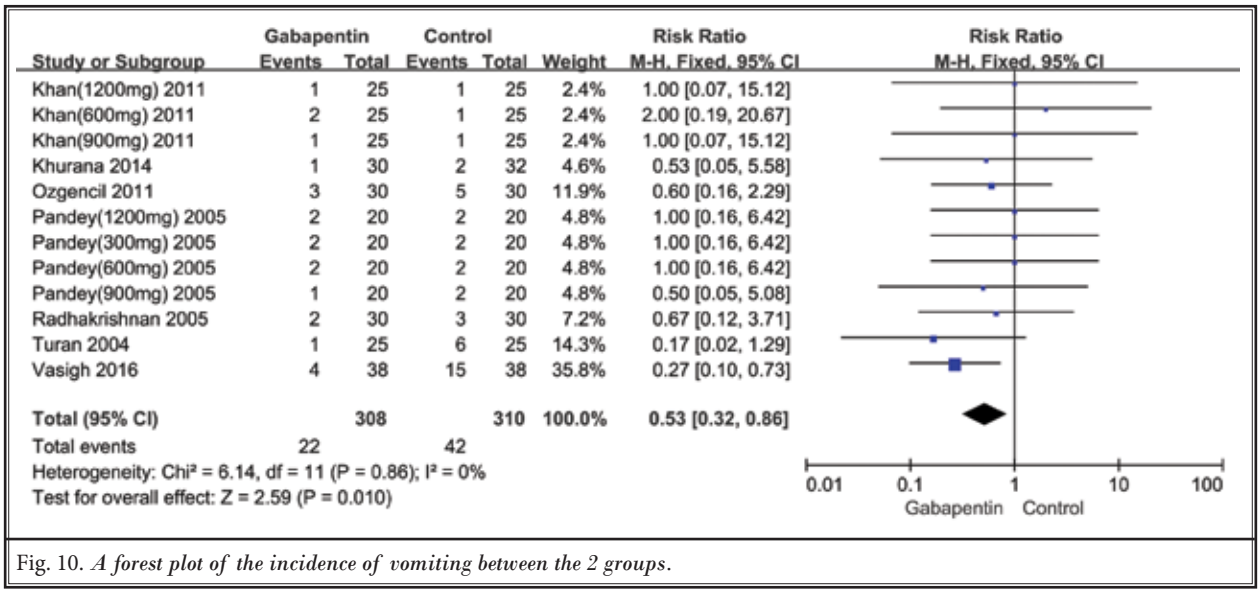

Fig. 10. *A forest plot of the incidence of vomiting between the 2 groups.*

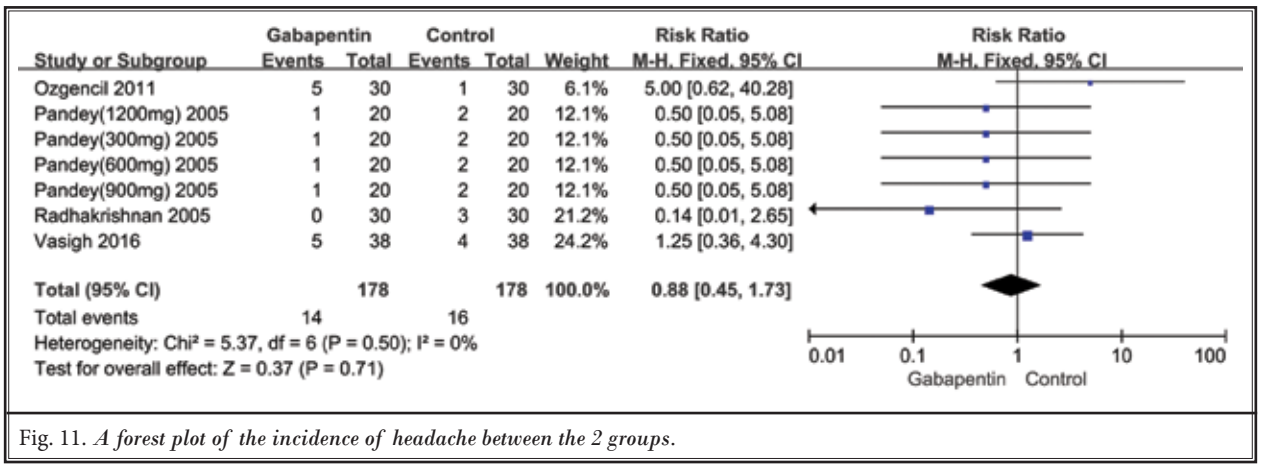

Fig. 11. *A forest plot of the incidence of headache between the 2 groups.*

(21,22,24,27). Compared with the control group, gabapentin did not significantly affect the incidence rate of headache. (RR = 0.88, 95% CI 0.45–1.73, $P = 0.71$; Fig. 11). No evidence of statistical heterogeneity was found in any of those studies ($\chi^2 = 5.37$, df = 6, $I^2 = 0\%$, $P = 0.50$).

Seven trials reported the incidence of dizziness (19-21,25,27). Compared with the control group, gabapentin did not significantly affect the incidence rate of dizziness (RR = 1.08, 95% CI 0.68–1.72, $P = 0.75$; Fig. 12). No evidence of statistical heterogeneity was found in any of the 7 studies ($\chi^2 = 4.84$, df = 6, $I^2 = 0\%$, $P = 0.56$).

The incidence of somnolence was reported by 7 trials (19,21,24,25,27). The pooled result showed a positive effect of gabapentin in all of the trials (RR = 2.52, 95% CI 1.36–4.67, $P = 0.003$; Fig. 13). No evidence of statistical heterogeneity was found in any of the studies ($\chi^2 = 5.94$, df = 6, $I^2 = 0\%$, $P = 0.43$).

Four studies reported the incidence rate of pruritus (21,24,25,27). Significant heterogeneity was not found, therefore a fixed-effects model was used ($\chi^2 = 0.29$, df = 3, $I^2 = 0\%$, $P = 0.96$). Compared with the control group, the incidence rate of pruritus was less in the gabapentin group (RR = 0.38, 95% CI 0.22–0.66, $P = 0.00$; Fig. 14).

Four studies reported the incidence rate of urinary retention (21,24,25,27). Significant heterogeneity was not found, thus a fixed-effects model was used ($\chi^2 = 4.20$, df = 3, $I^2 = 29\%$, $P = 0.24$). Compared with the

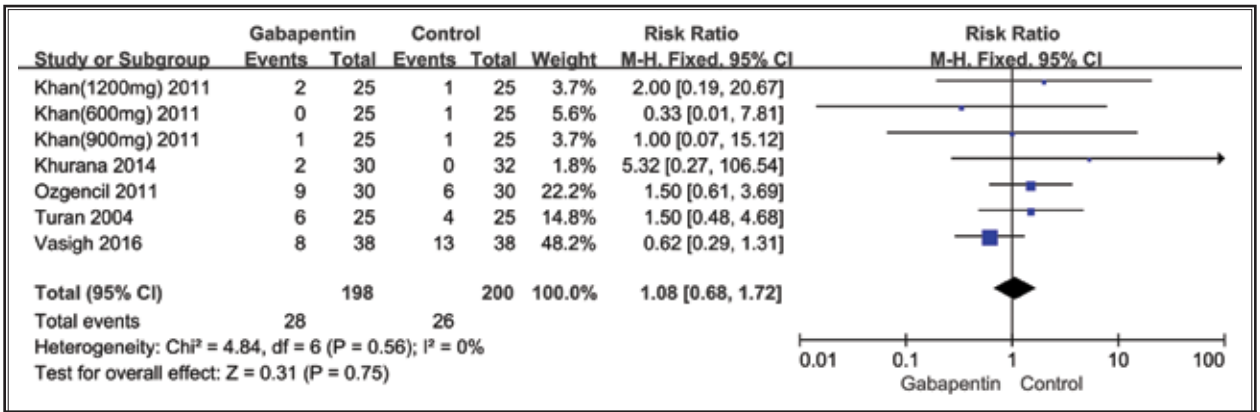

Fig. 12. *A forest plot of the incidence of dizziness between the 2 groups.*

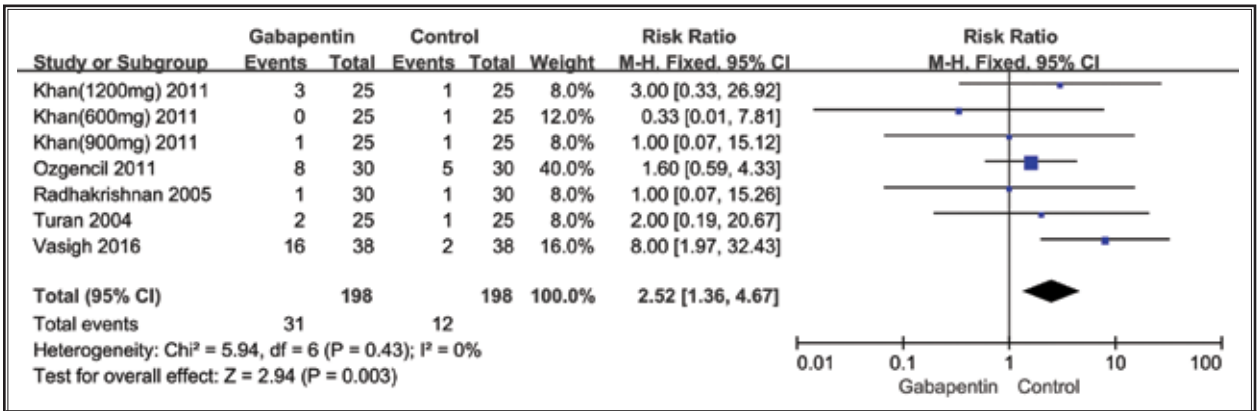

Fig. 13. *A forest plot of the incidence of somnolence between the 2 groups.*

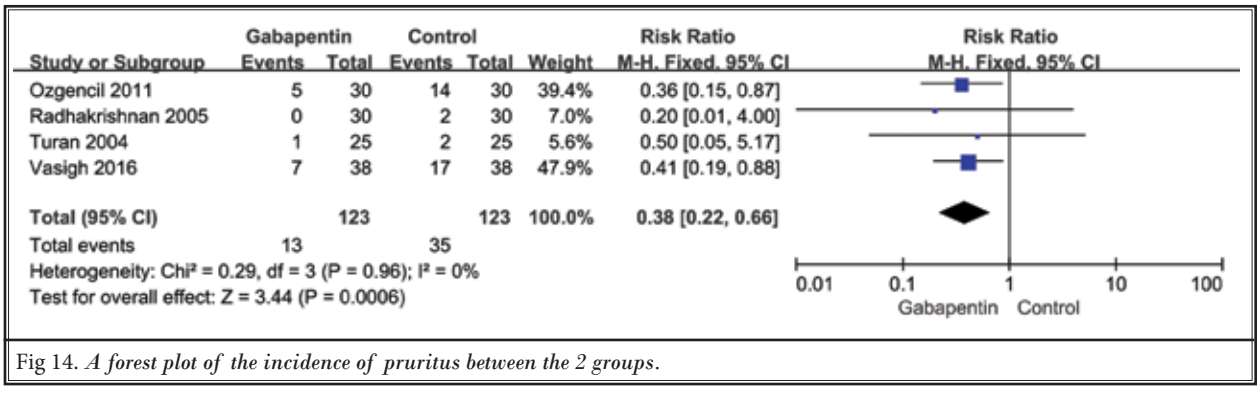

Fig 14. *A forest plot of the incidence of pruritus between the 2 groups.*

control group, gabapentin could significantly reduce the incidence rate of urinary retention (RR = 0.57, 95% CI 0.34–0.98, *P* = 0.04; Fig. 15).

Sensitivity Analysis and Publication Bias

Sensitive analysis by omitting one study in each turn indicated that the association of gabapentin with spinal surgery became significant after removing Radhakrishnan's study (24) (OR: -1.29, 95% CI: -1.46 to -1.12). None of the other results was altered in the sensitivity analysis. A funnel plot for the included studies is illustrated in Fig. 16; this plot shows a symmetrical shape.

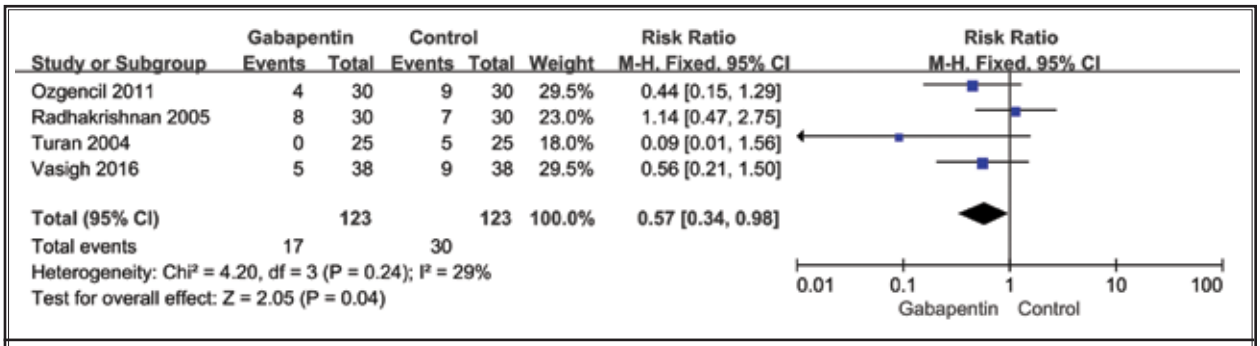

Fig. 15. *A forest plot of the incidence of urinary retention between the 2 groups.*

Discussion

The aim of this work was not only to evaluate the pain management of spinal surgery, but also to assess the opioid usage and incidence of adverse effects in the included RCTs. Although multimodal analgesia has been approved to improve patient outcomes in many surgical operations (28-31), as far as we know, this meta-analysis might be the first regarding gabapentin alone in the treatment of postoperative pain after spinal surgery. We perform this work to estimate whether, compared with the placebo, the use of gabapentin could significantly improve the clinical outcomes.

Our meta-analysis of the pooled data directed to evaluate the relevant literatures systematically and shed new light on the effectiveness of pre-emptive gabapentin in the management of pain and side effects in spinal surgery. Our overall results demonstrated that compared with the placebo, the administration of gabapentin could reduce the cumulative morphine consumption at 24 hours postoperatively. This result was similar to those of other studies (13,32,33).

In order to assess the effect of gabapentin in the relief of postoperative pain, the VAS scores were often employed in clinic. In this part, the postoperative VAS score at 2, 4, 6, 12, and 24 hours were used for pain assessment. The pooled data showed significant reductions in pain scores at all of the timepoints in the gabapentin group. This finding of our research is also consistent with those of previous studies (33,34).

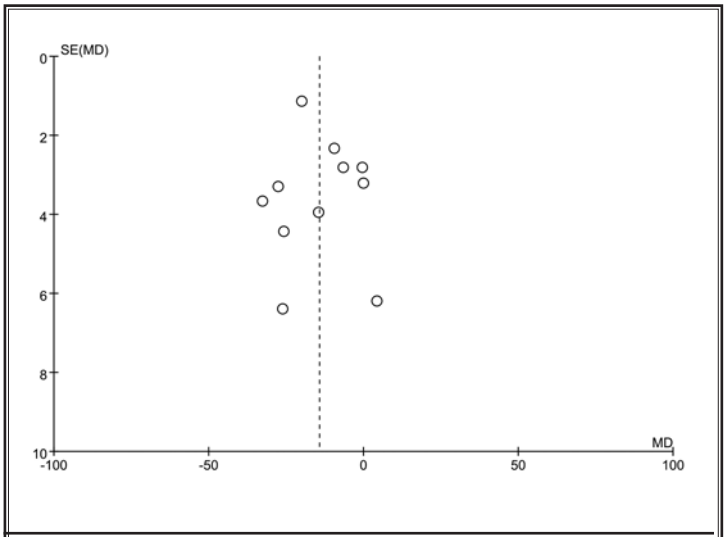

Fig. 16. *A funnel plot for publication bias.*

Nausea, headache, and dizziness were common complications in the postoperative period when gabapentin was applied. As shown in Fig. 9, 11, and 12, the incidence rate of these side effects appeared to increase in the control group, however, no statistically significant difference was found. Previous researches reported that gabapentin administration was related to the postoperative side effects (35), our meta-analysis was somewhat similar with the former studies. Regarding other side effects, such as vomiting, somnolence, pruritus, and urinary retention, we found that the incidence rates of vomiting, pruritus, and urinary retention in the gabapentin group were decreased significantly when compared to the placebo group. However, the incidence rate of somnolence was significantly increased in the gabapentin group. This finding was interesting, because the different use of analgesics and methods of anaesthesia might be related to the final result; the variety of sample sizes and operating methods might also explain this discrepancy.

Table 2. *Subgroup analysis.*

Subgroup or Outcomes	Studies	Effect Estimate			
		χ^2	MD and 95%CI	I^2 (%)	*P*
Different Region	3	10.10	-8.67 [-13.94, -3.40]	80	0.01
Different Dosage	3	1.41	-5.36 [-6.27, -4.45]	0	0.49
Age (< 45)	10	161.68	-5.74 [-7.61, -3.87]	93	0.00

Statistical heterogeneity was found in this study. Thus, a random-effects model was performed to evaluate the results. A subgroup analysis was carried out to find the source of heterogeneity (Table 2). Factors such as region differences, dosage discrepancy, and age differences caused the heterogeneity. Due to the inconsistency caused by very serious heterogeneity, the quality of evidence regarding VAS scores and opioid requirement was relatively low. Furthermore, all of the included studies were RCTs of high quality. Therefore, the overall quality of evidence and effect estimate was reliable.

Study Limitations

There were several potential limitations to our meta-analysis. Firstly, some factors, such as the type of spinal surgery and complications, may also play a vital role in the management of pain. Secondly, the administration time and dosages were various: the range was from 300 mg to 1200 mg, and the administration time was not consistent. Although our results demonstrate that cumulative opioid consumption and VAS scores in all of the time-points were dramatically decreased in the gabapentin group, we can hardly claim what the best dosages are from this work. Pandey et al (22) found that the best dose of gabapentin was 600mg. However, Khan et al (19) suggested that 900mg or 1200 mg of gabapentin appears more effective in the reduction of the pain scores. Thirdly, only 10 studies, with a total of 827 patients, were included in our study; if more RCTs had been included, the statistical efficacy of our analysis would increase. Fourthly, the included studies in this meta-analysis were written in English, which may cause important studies to be overlooked. More studies are needed to further investigate the best use of gabapentin.

Conclusion

This meta-analysis of RCTs reveals that pre-emptive utilization of gabapentin could significantly reduce postoperative VAS scores, postoperative morphine consumption at 24 hours, and the incidence rates of some adverse effects in spinal surgery.

Author Contributions

C.H. and M.J.K conducted the literature search and determined the studies for exclusion and inclusion. M.J.K. and J.X.M extracted data from the included studies, performed the meta-analysis, and drafted the manuscript. C.H. and X.L.M. conceived the idea of the study, designed the study, and critically revised the manuscript for important intellectual content. All of the authors reviewed the paper and approved the final manuscript.

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