Systematic Review and Meta-Analysis

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The use of gabapentin in the management of postoperative pain after total knee arthroplasty

A PRISMA-compliant meta-analysis of randomized controlled trials

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Abstract

Pain management after total knee arthroplasty (TKA) varies and has been widely studied in recent years. Some randomized controlled studies have carried out to evaluate the effects of gabapentin on pain relief after TKA. However, no solid result was made about it. The purpose of this Meta-Analysis of Randomized Controlled Trials (RCTs) was to estimate the overall effect of pain control of gabapentin versus placebo after a TKA. An electronic-based search using the following databases: PubMed, EMBASE, Ovid MEDLINE, ClinicalTrials.gov, and Cochrane Central Register of Controlled Trial from 1966 to June 2015. RCTs involving gabapentin and placebo for total knee arthroplasty were included. The meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Six trials with 859 participants met the inclusion criteria. The primary endpoint was cumulative narcotic consumption and the visual analog scale scores at 12 hours, 24 hours, and 48 hours, postoperatively. The knee flexion degree and treatment side effects were also compiled to evaluate the safety of gabapentin. After testing for the heterogeneity and publication bias among studies, data were aggregated for random-effects modeling when necessary. There was a significant decrease in morphine consumption at 12 hours (MD = –4.69, 95% CI: –7.18 to –2.21, $P = 0.0002$), 24 hours (MD = –5.30, 95% CI: –9.94 to –0.66, $P = 0.03$), and 48 hours (MD = –17.80, 95% CI: –31.95 to –3.64, $P = 0.01$), respectively. Compared with the control group, the rate of pruritus was less in the gabapentin group (RR 0.20, 95% CI 0.10 to 0.38, $P = 0.00$). In summary, the administration of gabapentin was effective in decreasing postoperative narcotic consumption and the incidence of pruritus. There was a high risk of selection bias and a higher heterogeneity of knee flexion range in this analysis. More high-quality large randomized controlled trials with long follow-up period are necessary for proper comparisons of the efficacy and safety of gabapentin with placebo.

Systematic review registration number: No.

Abbreviations: CIs = confidence intervals, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses, RCTs = randomized controlled trials, RR = relative risk, MD = mean difference, TKA = total knee arthroplasty, VAS = visual analog scale.

Keywords: gabapentin, meta-analysis, total knee arthroplasty

1. Introduction

Approximately >500,000 total knee arthroplasty (TKA) are performed in North America annually.[1] Pain is often successfully treated early in the disease process. However, poor control of postoperative pain can have negative effects on the pulmonary system and cardiovascular system, which leads to complications that delay discharge from hospital.

Pain management is often directed at enhancing pain relief and reducing narcotic requirements by multimodal analgesia.[2] Despite the multimodal approach, the postoperative pain is still a major issue in patient care after TKA, and some patients may develop intractable postoperative pain.[3,4] Given the various side effects of analgesics opioid, the use of an additional nonopioid agent is often needed.[5] One of the agents is gabapentin, which is a third-generation antiepileptic drug that selectively affects the nociceptive process.[6] It not only has the central and peripheral antalgic activity, but also has the relatively well-tolerated property.[7]

In the past several years, some randomized controlled studies were carried out to evaluated the effects of preemptive gabapentin before surgical as well as a combination preemptive and postoperative gabapentin.[8–11] Although some conclusions have been made, its role in postoperative pain relief after TKA has not been investigated in systematic review and meta-analysis. This work was to examine the evidence of the gabapentin systematically and make a comprehensive understanding of the efficacy and safety of gabapentin in the management of postoperative pain after TKA.

Editor: Kazuo Hanaoka.

CH, X-dL, H-qJ contributed equally to this study.

The authors have no funding and conflicts of interest to disclose.

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Medicine (2016) 95:23(e3883)

Received: 17 March 2016 / Received in final form: 12 May 2016 / Accepted: 16 May 2016

Published online 1 May 2016

http://dx.doi.org/10.1097/MD.0000000000003883

2. Methods

This study was reported according with the guideline of PRISMA statement. Ethical approval and patient written informed consent were not required owing to that this was a meta-analysis of previously published studies. The literature search was conducted by following databases: Medline, Cochrane database, ClinicalTrials.gov, PubMed, and Embase. The following keywords including pain management, postoperative pain, total knee arthroplasties, total knee replacement, and gabapentin were used for searching.

1. Inclusion criteria. Studies were considered eligible for inclusion if they met the following criteria: Study design: Randomized controlled trials (RCTs) with placebo report in English. Population: Patients with total knee arthroplasties. Intervention group: Gabapentin. Control group: Placebo. Outcomes: Reported at least one of the following items: Postoperative consumption of morphine; pain scores (VAS); knee flexion degree and treatment side effects.

2. Exclusive criteria. Patients were excluded from the meta-analysis if they had neoplastic etiology, infection, traumatic fracture, metal sensitivity, or mental diseases.

3. Selection criteria. Eligibility assessment was performed independently in an unblended standardized manner by 2 reviewers. Disagreements between reviewers were resolved by consensus. Assessment of risk bias was based on the Cochrane collaboration's tool.[12] The quality of the randomized controlled trials was assessed by Funnel plots.

4. Data extraction. Data were extracted from the enrolled literatures by 2 authors independently. The extracted data included: publication data, the first author's name, the size of sample, gabapentin dose, pain scores, and side effects.

5. Statistical analysis. The data was analyzed by RevMan 5.3 (The Cochrane Collaboration, Oxford, United Kingdom). Heterogeneity was estimated depending on the value of P and I^2 using the standard chi-square test. $P<0.10$ and $I^2>50\%$ were defined as having significant heterogeneity. Then, a random-effects model was applied for data analysis. A fixed-effects model was used when no significant heterogeneity was found. The results of the meta-analysis studies were expressed as the standardized mean difference with 95% confidence intervals (CIs) for continuous outcomes such as narcotic consumption and pain scores and relative risk with 95% CIs for dichotomous data such as nausea and other side effects. Differences in means were considered significant with a $P<0.05$.

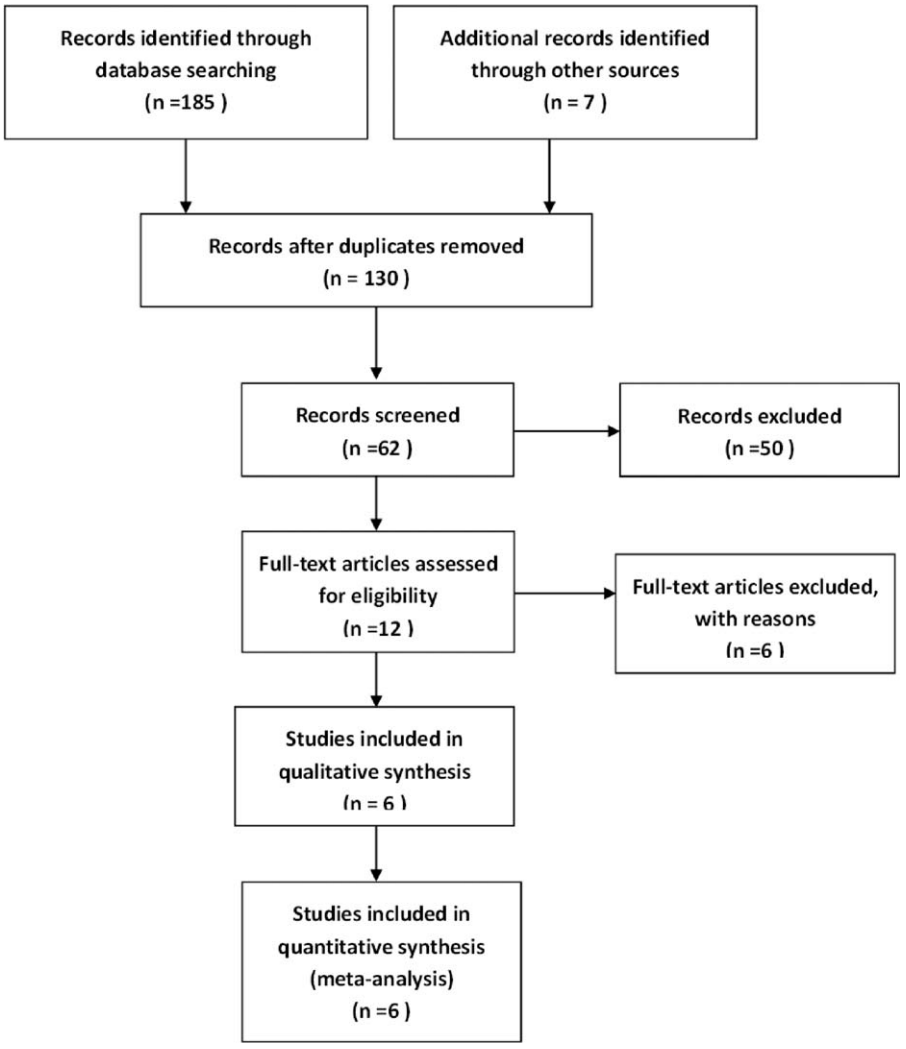

Figure 1. The selection of literature for included studies.

Table 1

Characteristics of included studies.

Clinical trials	Age (y)	Gender (M/F)	Location	No. of patients gabapentin/control	Dose of gabapentin	Time of gabapentin administration
Clarke 2009 Pre	60.7	5/9	Canada	7/7	600 mg preoperatively	2 h preoperatively
Clarke 2009 HD	63.1	4/10	Canada	7/7	600 mg preoperatively and 900 mg 9postoperatively	2 h preoperatively, then every 8 h postoperatively
Clarke 2009 MD	64.5	5/9	Canada	7/7	600 mg preoperatively and 600 mg postoperatively	2 h preoperatively, then every 8 h postoperatively
Clarke 2009 LD	60.6	6/9	Canada	8/7	600 mg preoperatively and 300 mg postoperatively	2 h preoperatively, then every 8 h postoperatively
Clarke 2014	62.8	89/100	Canada	95/84	600 mg	2 h preoperatively
Gencer 2014	63.1	16/24	Turkey	20/20	1200 mg	1 h preoperatively
Lunn 2015 HD	68	83/115	Denmark	99/99	1300 mg	2 h preoperatively
Lunn 2015 LD	69.5	87/112	Denmark	100/99	900 mg	2 h preoperatively
Paul 2011	61.7	31/49	Canada	44/41	600 mg	2 h preoperatively
Paul 2013	62.8	37/64	Canada	52/49	600 mg	2 h preoperatively

3. Results

1. Literature search. A total of 192 potential studies were identified with the first search strategy. Of these, 186 reports were excluded according to the eligibility criteria. Six studies were included.[13–18] These studies involved a total of 420 patients in the control group and 439 patients in the gabapentin group. In 5 trials, gabapentin was given preoperatively only,[13–17] whereas in 1 trial gabapentin was administered preoperatively and postoperatively.[18] Clarke 2009 Pre, Clarke 2009 HD, Clarke 2009 MD, and Clarke 2009 LD was the same trial, in which there were 5 groups, and we divided this trial into 4 different comparisons (gabapentin vs placebo preoperatively; gabapentin 300 mg vs placebo postoperatively; gabapentin 600 mg vs placebo postoperatively; and gabapentin 900 mg vs placebo postoperatively). Lunn 2015 HD and Lunn 2015 LD was also the same trial, in which there were 3 groups, and we divided this trial into 2 different comparisons (gabapentin 1300 mg vs placebo; and gabapentin 900 mg vs placebo) (Fig. 1).

2. Study characteristics. The characteristics of the included gabapentin studies are reported in Table 1. Statistically similar baseline characteristics were observed between the gabapentin and placebo groups.

3. Risk of bias assessment. According to the Cochrane collaboration's tool for assessing risk of bias in randomized controlled trials, all the included trials had a low risk of bias (Fig. 2).

4. Outcomes for meta-analysis.

Postoperative Narcotic Requirements at 12 hours. Details regarding narcotic consumption at 12 hours were available in 6 trials.[16–18] There was no significant heterogeneity ($\chi^2=3.65$, $df=5$, $I^2=0\%$, $P=0.60$); therefore, a fixed-model was performed. The overall pooled results from meta-analysis demonstrated that compared with placebo, gabapentin could significantly reduce the postoperative narcotic consumption (MD = –4.69, 95% CI: −7.18 to –2.21, $P=0.0002$; Fig. 3).

Postoperative Narcotic Requirements at 24 hours. Details regarding narcotic consumption at 24 hours were available in 8 trials.[13,14,16–18] There was no significant heterogeneity ($\chi^2=10.0$, $df=7$, $I^2=30\%$, $P=0.19$); a fixed-model was performed. The overall pooled results from meta-analysis demonstrated that compared with placebo, gabapentin could also significantly reduce the postoperative narcotic consumption (MD = –5.30, 95% CI: −9.94 to –0.66, $P=0.03$; Fig. 4).

Postoperative Narcotic Requirements at 48 hours. Details regarding narcotic consumption at 48 hours were available in 8 trials.[13–15,18] Significant heterogeneity was found ($\chi^2=41.58$, $df=7$, $I^2=83\%$, $P=0.00$); a random-model was performed. The

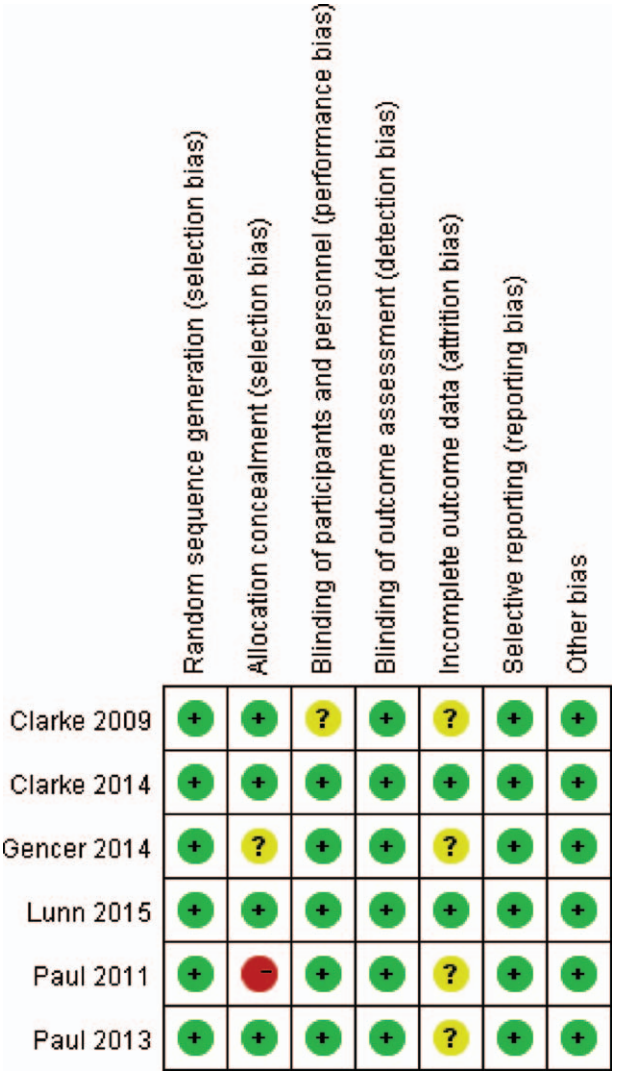

Figure 2. The summary of bias risk of randomized controlled trials.

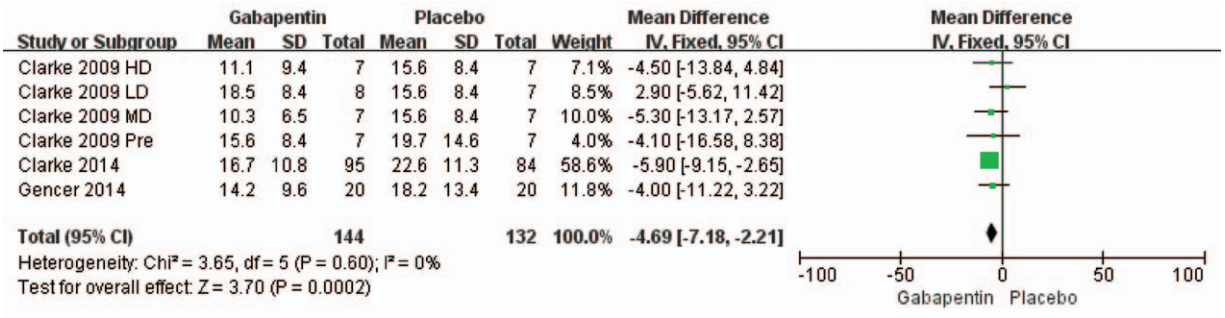

Figure 3. Forest plot of postoperative narcotic consumption at 12 hours between 2 groups.

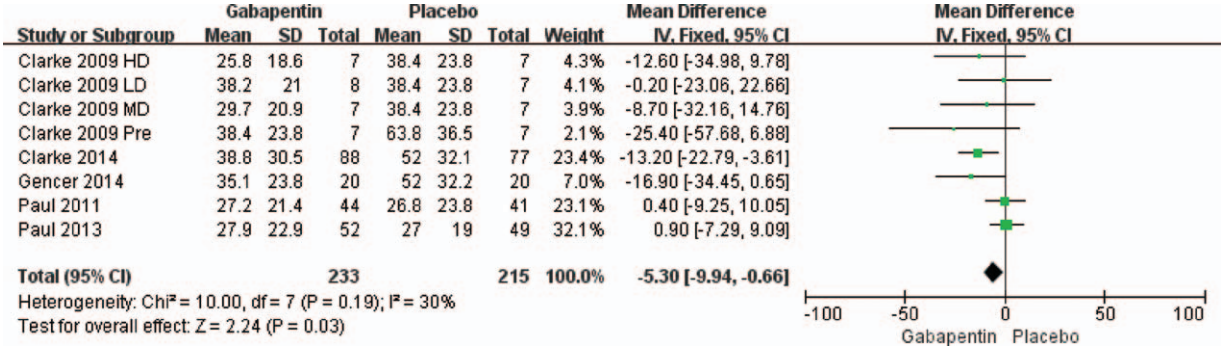

Figure 4. Forest plot of postoperative narcotic consumption at 24 hours between 2 groups.

overall pooled results from meta-analysis demonstrated that compared with placebo, gabapentin could also significantly reduce the postoperative narcotic consumption (MD = –17.80, 95% CI: –31.95 to –3.64, $P = 0.01$; Fig. 5).

Postoperative visual analog scale (VAS) at 12 hours. Five trials reported VAS at 12 hours. [16,18] Significant heterogeneity was not found, a fixed-model was used ($\chi^2 = 3.52$, $df = 4$, $I^2 = 0\%$, $P = 0.47$). Compared with placebo, gabapentin could not significantly reduce the VAS at 12 hours (MD = – 5.90, 95% CI: –12.96 to 1.16, $P = 0.10$; Fig. 6).

Postoperative VAS at 24 hours. nine trials reported VAS at 24 hours.[13–16,18] There was no significant heterogeneity ($\chi^2 = 7.01$, $df = 8$, $I^2 = 0\%$, $P = 0.54$); therefore, a fixed-model was performed. The overall pooled results from meta-analysis demonstrated that compared with placebo, no significant difference was found in gabapentin groups (MD = –0.16, 95% CI: –2.88 to 2.57, $P = 0.91$; Fig. 7).

Postoperative VAS at 48 hours. Eight trials reported VAS at 48 hours.[13–15,18] Significant heterogeneity was not found; a fixed-model was used ($\chi^2 = 4.01$, $df = 7$, $I^2 = 0\%$, $P = 0.78$). The pooled results demonstrated that compared with placebo, no significant difference was found in gabapentin groups (MD = –0.19, 95% CI: –2.18 to 1.79, $P = 0.78$; Fig. 8).

Knee flexion range. Five studies showed postoperative knee flexion range.[13,14,16–18] Significant heterogeneity was found, so a random-model was applied ($\chi^2 = 27.19$, $df = 4$, $I^2 = 85\%$, $P =$

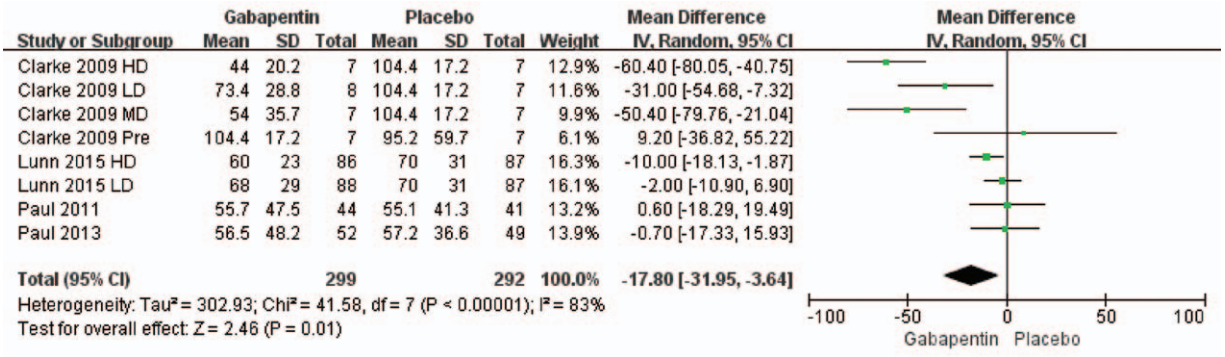

Figure 5. Forest plot of postoperative narcotic consumption at 48 hours between 2 groups.

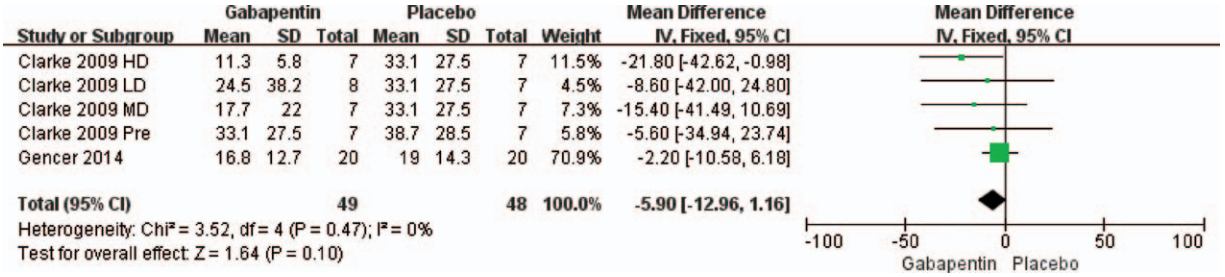

Figure 6. Forest plot of postoperative VAS at 12 hours between 2 groups. VAS, visual analog scale.

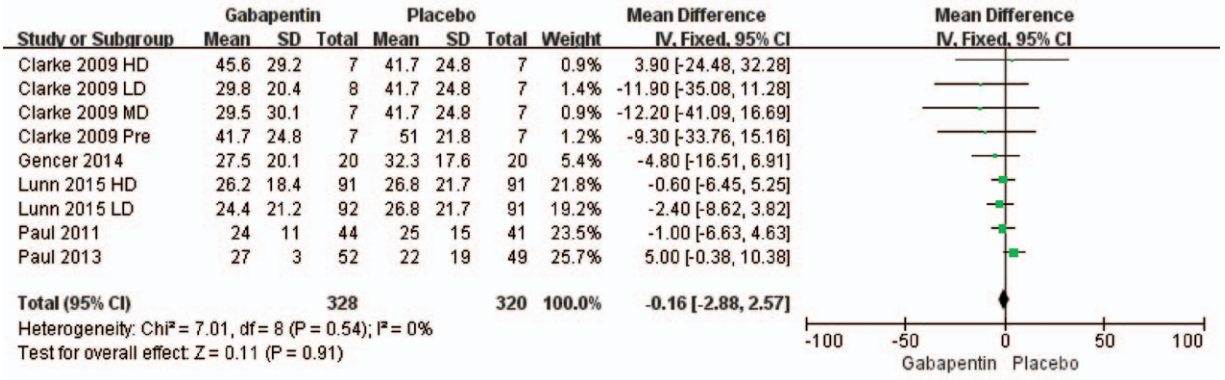

Figure 7. Forest plot of postoperative VAS at 24 hours between 2 groups. VAS, visual analog scale.

0.00). No significant difference in knee flexion degree was found between gabapentin groups and placebo groups (MD = 1.17, 95% CI: −5.45 to 7.80, $P = 0.73$; Fig. 9).

3.1. Adverse effects

The most commonly reported adverse effects in the trials included in our study were nausea; it was reported in 5 studies.[13,14,16–18] Significant heterogeneity was not found, a fixed-model was used ($\chi^2 = 1.51$, $df = 4$, $I^2 = 0\%$, $P = 0.83$). Compared with the control group, no significant difference was found in gabapentin groups (RR 0.76, 95% CI 0.70–1.29, $P = 0.74$; Fig. 10).

Four studies reported the incidence rate of pruritus.[13,14,17,18] Significant heterogeneity was not found; a fixed-model was used ($\chi^2 = 1.24$, $df = 3$, $I^2 = 0\%$, $P = 0.74$). Compared with the control group, the rate of pruritus was less in the gabapentin group (RR 0.20, 95% CI 0.10–0.38, $P = 0.00$; Fig. 11).

Four studies reported the incidence rate of sedation.[13,14,17,18] Significant heterogeneity was not found; a fixed-model was used ($\chi^2 = 0.51$, $df = 3$, $I^2 = 0\%$, $P = 0.92$). Compared with the control group, no significant difference was found in gabapentin groups (RR 1.13, 95% CI 0.69–1.83, $P = 0.63$; Fig. 12).

Three studies reported the incidence rate of dizziness.[13,17,18] Significant heterogeneity was found; a random-model was applied ($\chi^2 = 10.46$, $df = 2$, $I^2 = 81\%$, $P = 0.00$). Compared with the control group, no significant difference was found in gabapentin groups. (RR 0.41, 95% CI 0.11–1.51, $P = 0.18$; Fig. 13).

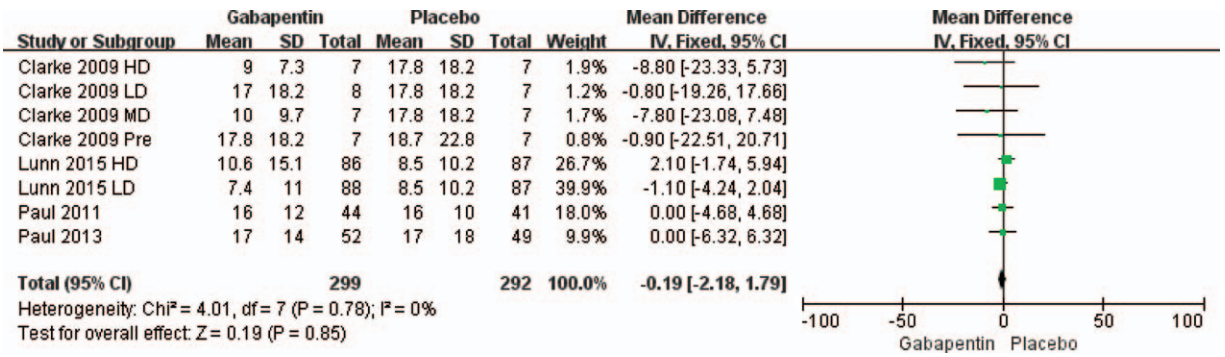

Figure 8. Forest plot of postoperative VAS at 48 hours between 2 groups. VAS, visual analog scale.

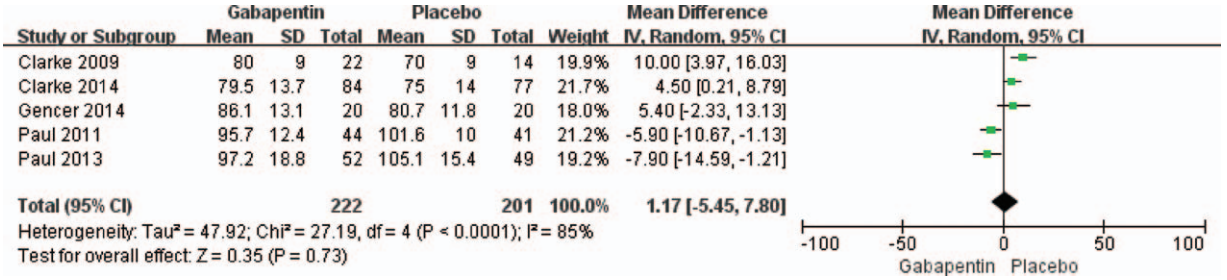

Figure 9. Forest plot of postoperative Knee flexion range between 2 groups.

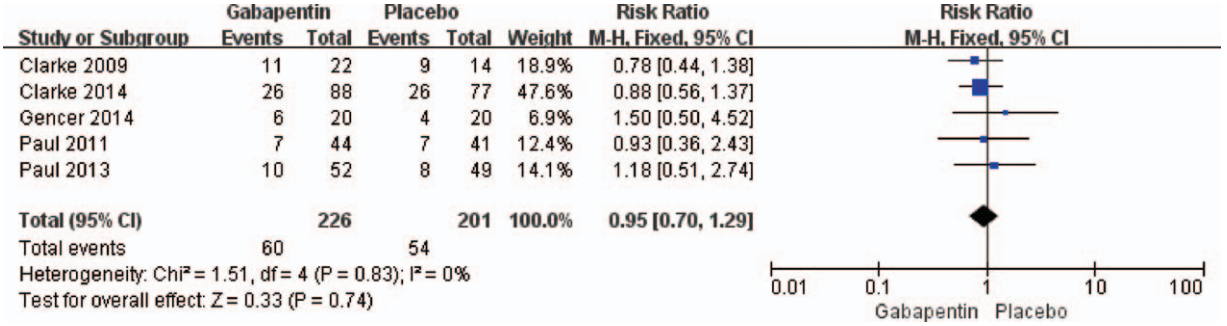

Figure 10. Forest plot of incidence of nausea between 2 groups.

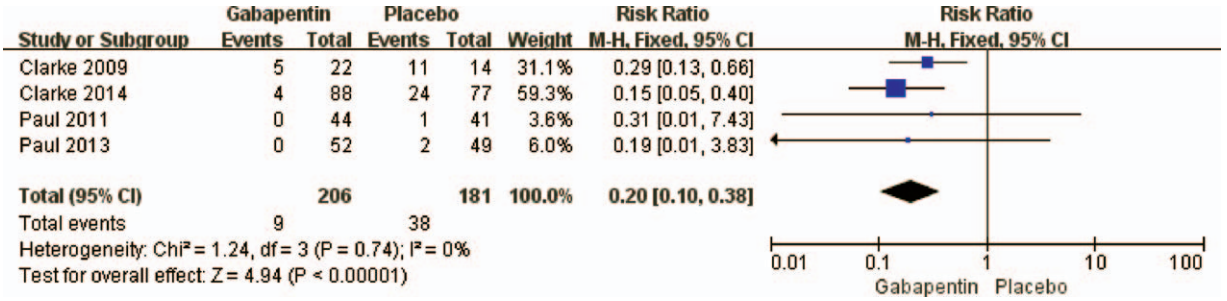

Figure 11. Forest plot of incidence of pruritus between 2 groups.

4. Discussion

This work was to review the literature systematically and make a comprehensive understanding of the efficacy of gabapentin in the management of postoperative pain after TKA. Our data analysis showed that the consumption of cumulative narcotic in the gabapentin group were reduced significantly when compared with the control group at 12 hours, 24 hours, and 48 hours postoperatively. This result is in accordance with previous studies about the effect of gabapentin in various operations.[9,19,20]

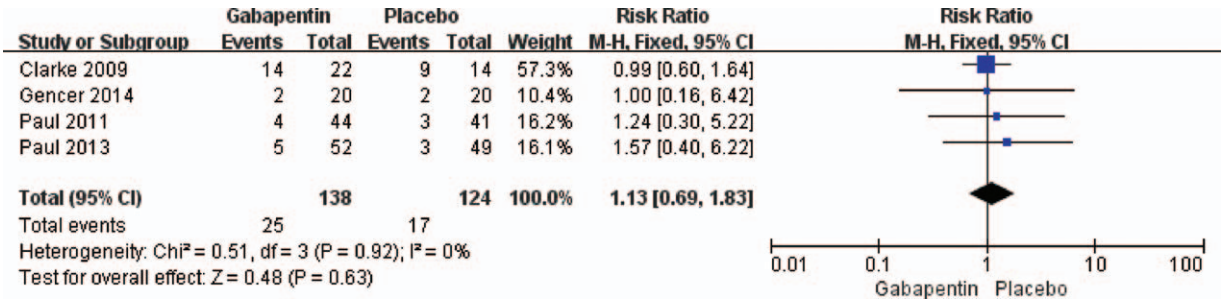

Figure 12. Forest plot of incidence of sedation between 2 groups.

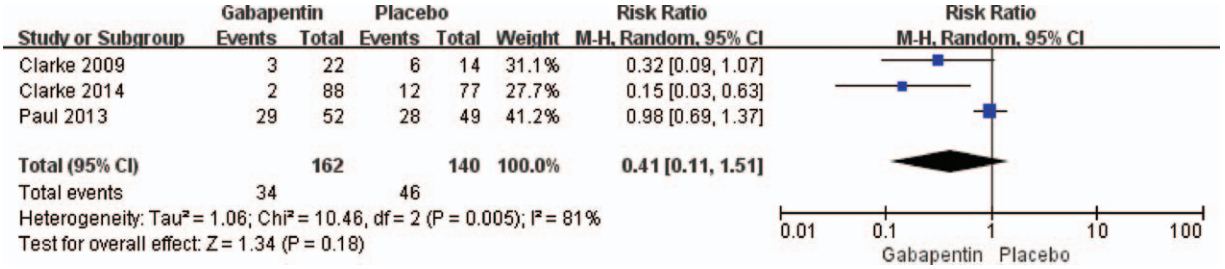

Figure 13. Forest plot of incidence of dizziness between 2 groups.

VAS score is usually used to estimate the effect of gabapentin on postoperative pain relief. In our study, the 12, 24, and 48 hours postoperatively were selected as point-in-time for comparison. However, no significant reduction in VAS score was found in the gabapentin group compared with placebo group at all 3 time points. The finding of our research is different with the former studies.[20,21] This could be explained by the discrepancy of surgical procedure and the difference of sample sizes.

Knee flexion degree postoperatively is also a vital indicator to evaluate the result of TKA. Unfortunately, compared with placebo, gabapentin cannot increase the knee flexion range in this study. This could be associated to the postoperative VAS scores. Without the good analgesic effect, patients can hardly do excises in their operated limb.

Pruritus is one of side effect during the administration of gabapentin. As shown in Fig. 11, gabapentin can significant decrease the incident rate of postoperative pruritus. This is similar with the former research.[22] Other side effects such as nausea, sedation, and dizziness in gabapentin group share the same incident rate with the placebo group. It is still vague that whether these adverse effects are dose-related to the usage of gabapentin.

To the best of our knowledge, this study was the first meta-analysis regarding gabapentin in the management of postoperative pain after TKA. All the studies were based on prospective studies, which overcome the shortcomings of retrospective or observational studies. The limitations to our findings are the small sample sizes and various research methods of included literature, which might affect the overall results. Almost all the included literatures were published by anesthetists, some important details usually concerned by orthopedics such as surgical approach, technique of incision, methods of fixation, and type of implant were not reported in those papers. It is believe that all of these factors have the ability to change the degree of postoperative pain and they need to be taken into account in the further study.

Another limitation was that the dosages and medication time of gabapentin were varied. Though clinical administration dose ranged from 600 to 1300 mg in trials, it seems that diverse doses of gabapentin cannot have an effect on VAS scores significantly. There was controversy over the optimal dosage of oral gabapentin. Pandey et al [23] suggested that 600 mg of gabapentin was the most optimal regimen; however, Khan et al [24] found that morphine consumption was less, pain scores were lower. We are unable to comment on the preferred dosages from this meta-analysis, yet it seems that doses as low as 600 mg are as effective as 1200 mg.

5. Conclusion

This meta-analysis of prospective studies witness that gabapentin was efficacious in reduction of postoperative narcotic requirements and rate of pruritus after TKA.

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