

Original Article

Gabapentin can decrease pain intensity for patients undergoing total knee arthroplasty: a systematic review meta-analysis

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Abstract: Objective: Total knee arthroplasty (TKA) has always been associated with moderate to severe pain postoperatively. Gabapentin exhibits antiallodynic and antihyperalgesic properties that can reduce pain intensity when adjuvant to multiple postoperative analgesia. The purpose of this systematic review and meta-analysis of randomized controlled trials (RCTs) was to evaluate the efficacy and safety of gabapentin for pain control after TKA. Methods: In May 2016, electronic databases as follows: Embase, PubMed, CENTRAL (Cochrane Controlled Trials Register), Web of Science, Google Scholar, Chinese National Knowledge Infrastructure (CNKI) and Chinese Wanfang databases. Visual analogue scale (VAS) score after TKA with rest or mobilization at 24 h and 48 h were compiled to assess the efficacy of pain control after TKA. Cumulative morphine consumption at 24 h and 48 h and active knee flexion at day 3 and day 4 were also compiled to assess the morphine-saving and knee function. Complications such as dizziness, pruritus, vomiting, nausea and sedation were also compiled to assess the safety of gabapentin. Stata 12.0 software was used for the meta-analysis. Results: Seven clinical trials with 735 patients were finally included in the meta-analysis. The pooled results indicated that gabapentin can decrease VAS score with rest at 24 h (MD=-3.84; 95% CI -5.47 to -2.20; P<0.001) and at 48 h postoperatively (MD=-1.98; 95% CI -3.55 to -0.40; P=0.014) with statistically significant when compared to control group. Pooled results indicated that preoperative administration gabapentin can decrease the VAS score with mobilization at 24 h postoperatively (MD=-8.85; 95% CI -11.55 to -6.15; P<0.001) and 48 h postoperatively (MD=-2.35; 95% CI -4.40 to -0.29; P=0.025). These results indicated that the perioperative administration of gabapentin decreases the cumulative morphine consumption at 24 h (MD=-11.99; 95% CI -15.75 to -8.24; P=0.000) and 48 h (MD=-7.79; 95% CI -17.75 to -7.95; P=0.126). Furthermore, gabapentin decreased the rate of postoperative dizziness and pruritus with statistically significant. Conclusion: In summary, gabapentin perform better pain control with rest or mobilization in early phase, increase active knee flexion and exert opioid-sparing effect when adjuvant to multiple postoperative analgesia after TKA. Moreover, gabapentin can also decrease the opioid-related complications.

Keywords: Gabapentin, total knee arthroplasty, pain management, randomized controlled trials, meta-analysis

Introduction

Although total knee arthroplasty (TKA) is indicated for effective treatment option for patients with symptoms of pain caused by osteoarthritis or rheumatic arthritis (RA) of the knee, however, the procedure itself is associated with moderate to severe pain during the early period after the operation [1]. It is reported that patients after TKA will underwent more pain than that of any other orthopedic surgery [2]. Moreover, the pain following TKA is especially intense during mobilization and thus may limit-

ed the mobilization of patients and increase the bed-related complications. Resuming ambulation as soon as possible after the TKA can decrease the occurrence of deep venous thrombosis (DVT) and the economic cost of recovery [3]. Recently, the sensitization of peripheral nociceptive nerve terminals and central neurons in surgery have received more and more attention to anesthetist [4].

Multimodal analgesia is currently the standard perioperative pain management, which aiming at enhancing pain relief and decreasing opioid

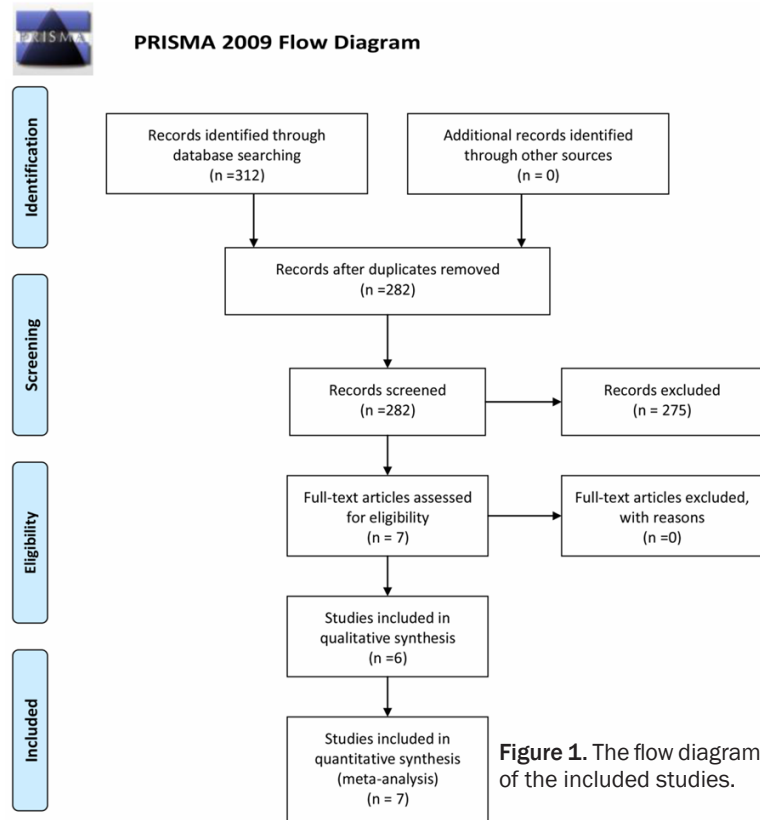


Figure 1. The flow diagram of the included studies.

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consumption meanwhile. A variety of modalities have been administrated to reduce postoperative pain after TKA, including femoral nerve block, local infiltration analgesia, and gabapentin [5, 6]. Though femoral nerve block show better pain control after TKA, it is widely accepted that some patients will also underwent moderate pain after TKA [7]. Woolf and Chong have proposed that antihyperalgesic drugs such as gabapentin can be used to reduce severe pain after TKA [8]. Recently, many studies have compared gabapentin with a placebo to manage pain after TKA. However, the results of these studies are contradictory. There is no consensus regarding the efficacy of gabapentin for managing postoperative pain after TKA. We therefore searched electronic databases and conducted a meta-analysis to identify the clinical outcome and safety of gabapentin in reducing pain intensity after TKA.

Materials and methods

Search strategy

Electronic databases as follows: Embase, PubMed, CENTRAL (Cochrane Controlled Trials Re-

gister), Web of Science, Google Scholar, Chinese National Knowledge Infrastructure (CNKI) and Chinese Wanfang databases were searched from 1990 to May 2016. The reason may the first clinical study about the gabapentin was researched in the year of 1990. The search strategies is: ((((((total knee replacement) OR total knee arthroplasty) OR TKA) OR TKR) OR "Arthroplasty, Replacement, Knee" [Mesh])) AND gabapentin. Furthermore, the reference lists of the identified literature and grey literature were also scanned to identify any initially omitted studies. Two reviewers (Da Gang Zhang and Kun Peng) independently searched the databases and selected the relevant articles according to the inclusion criteria, and conflicts were resolved by the third reviewer (Guang Lin Wang) or discussion.

Inclusion criteria and study selection

Inclusion criteria: (1) randomized controlled trials (RCTs); (2) patients who underwent a primary unilateral TKA, since bilateral TKA is more painful than unilateral TKA; (3) interventions, including gabapentin with a control (placebo or nothing) when adjuvant to multiple postoperative analgesia; and (4) reported outcomes, including postoperative VAS pain with rest or mobilization at 24 h and 48 h, cumulative morphine consumption at 24 h and 48 h and active knee flexion at days 2 and day 3, as well as the incidence of pruritus, vomiting, dizziness, sedation and nausea. Exclusion criteria: studies of cadavers or artificial models, non-RCTs, letters, comments, editorials, practice guidelines or other studies without one of the above outcomes.

Data abstraction and quality assessment

All of the searched literatures were independently screened by two reviewers. Most of the articles were excluded according to the title or abstract, and disagreements were resolved by discussion or consult to senior reviewer.

Table 1. The general characteristic of the included studies

Clinical trial	Country	Number of patients (G/C)	Mean age (G/C, yr)	Male/Female	Anesthesia
Lunn et al 2015	Denmark	195/96	67/70/69	130/168	Lumbar spinal anesthesia
Paul et al 2013	Canada	52/49	62.1/63.5	19/18	Spinal anesthetic
Clarke et al 2014	Canada	94/85	62.9/62.8	42/47	NS
Clarke et al 2009	Canada	29/7	63.9/57.3/65.8/62.33/60.7	14/22	Spinal anesthesia
Zhou et al 2013	China	20/20	NS	NS	General anesthesia
Guo et al 2015	China	24/24	58.2/59.3	34/12	General anesthesia
Wang 2010	China	20/20	38/36	28/12	General anesthesia

The following data were extracted and recorded in a Microsoft Excel: (1) the baseline of the included studies including age, number of patients, the dose and time to administration of gabapentin; (2) intraoperative and postoperative analgesia; and (3) the VAS score with rest or mobilization at 24 h and 48 h, the rates of pruritus, vomiting, dizziness, sedation and nausea, active knee flexion and the cumulative morphine consumption by 24 h and 48 h. The risk of bias for each RCT was evaluated using the Cochrane Collaboration's Risk of Bias Tool and described in "low bias", "unclear" and "high bias".

Statistical analysis

Continuous outcomes such as the VAS score with rest or mobilization at 24 h and 48 h, the cumulative morphine consumption at 24 h and 48 h, and active knee flexion were expressed as the mean difference (MD) with the respective 95% CIs. Discontinuous outcomes (i.e., the rate of pruritus, vomiting, dizziness, sedation and nausea) were expressed as the relative risk (RR) with 95% CIs. Statistical significance was set at $P < 0.05$. Stata software, version 12.0 (Stata Corp., College Station, TX) was used for the meta-analysis. Statistical heterogeneity was tested using the chi-squared test and I^2 statistic. A chi-squared test scoring $I^2 > 50\%$ was considered suggestive of statistical heterogeneity. Publication bias was tested by funnel plot and Begg's test, P value drawn from Begg's test exceed 0.05 considered no publication bias.

Results

Search results

In the initial search, we identified 312 potentially relevant studies, of which 30 duplicates

were removed by Endnote Software (**Figure 1**). According to the inclusion criteria, 275 studies were excluded after reading the titles and abstracts. Finally, we included seven clinical trials with 735 patients in the meta-analysis [10-16]. In the included studies, two articles were produced by the same team; however, after carefully reading the literature, we determined that the methods and the patients were different. Therefore, both studies were included in our analysis. The characteristics of the included studies are shown in **Table 1**, and the dose and time to administration of gabapentin are shown in **Table 2**. In the included studies, a total of 735 TKAs were performed, and the number of studies using gabapentin analgesia and a control group were 434 and 301, respectively. Two articles were published in 2009 [12, 13]; one was published in 2010 [10], and the others were published from 2010 [11, 14-16]. The participants in the five studies were mostly elderly, but one study included young patients. The age of the patients ranged from 36 to 70 years old. There were 263 male patients and 298 female patients. The dose of gabapentin ranged from 400 mg/d to 600 mg/d preoperatively and from 200 mg/d to 400 mg/d postoperatively. The intraoperative analgesia consisted of local infiltration, general analgesia and spinal analgesia. The postoperative analgesia included acetaminophen, patient controlled analgesia (PCA), and morphine or celecoxib; details can be seen in **Table 2**. Five RCTs introduced randomization; only two trial did not imply detailed random sequence generation. Two studies did not introduce concealment. The risk of bias can be seen in **Figures 2** and **3**.

Results of the meta-analysis

VAS score with rest: Ten studies with 683 patients provided a VAS score with rest at 24 h

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Table 2. The methods that management the pain during TKA and postoperative

Clinical trial	Dose of gabapentin	Intraoperative analgesai	Postoperative analgesics
Lunn et al 2015	Preoperatively and 400 mg on the day of surgery, thereafter 400 mg at 8:00 AM and 900 mg at 10:00 PM preoperatively 300 mg at 10:00 PM, thereafter 300 mg at 8:00 AM and 600 at mg 10:00 PM	Local infiltration analgesia (LIA) was performed intraoperatively with 150 ml ropivacaine 0.2% with epinephrine (10 µg/ml)	Acetaminophen 2 g and celecoxib 200 mg were administered regularly at 8:00 AM and 10:00 PM
Paul et al 2013	Gabapentin 600 mg po preoperatively followed by 200 mg po every eight hours for two days	Hyperbaric bupivacaine combined with fentanyl and no systemic opioid or local infiltration	Intravenous PCA morphine for three days, acetaminophen 1,000 mg po, and ketorolac 15 mg iv every six hours.
Clarke et al 2014	Gabapentin 600 mg p.o 2 h before surgery	Regional anaesthesia block area where an i.v. cannula was inserted and an infusion of i.v. lactated Ringer's solution was started at a rate of 100 ml h ⁻¹	PCA morphine device, and continuing every 6 h for the next 24 h
Clarke et al 2009	Preoperative GBP 600 mg/postoperative GBP 100 mg three times per day, preoperative GBP 600 mg/postoperative GBP 200 mg three times per day and preoperative GBP 600 mg/postoperative GBP 300 mg three times per day	Standard postoperative regimen of celecoxib 200 mg every 12 h for four days as well as an intravenous PCA morphine pump	Standard postoperative regimen of celecoxib 200 mg every 12 h for four days as well as an intravenous PCA morphine pump
Zhou 2013	Gabapentin 1200 mg, 2 h before surgery	Midazolam 3 mg, fentanyl 2~3 µg/kg, propofol 1.5~2 mg/kg vecuronium bromide 0.1 mg/kg to induce anesthesia and maintain by propofol 10 mg/kg/h and fentanyl 2~12 µg/kg	PCA fentanyl in dose of 15 µg
Guo 2015	Gabapentin 400 mg, 12 h before surgery	NS	Celecoxib and paracetamol and tramadol
Wang 2010	600 mg/day preoperative 8~12 h and 400 mg/kg postoperative 4 h	Remifentanyl 3.5 g/ml	Fentanyl 0.05 mg and flurbiprofen 50 mg

Gabapentin for pain control after TKA

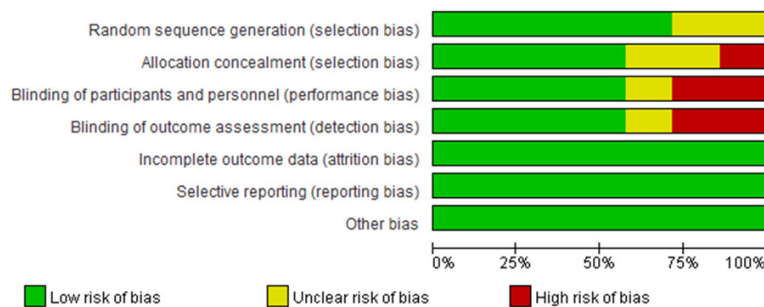


Figure 2. The summary of bias of the included studies.

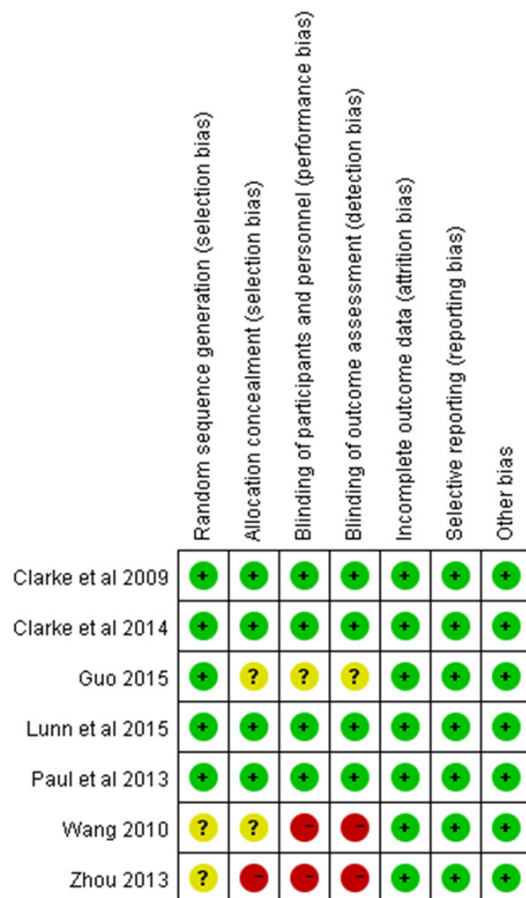


Figure 3. The bias of each included studies.

after TKA. Pooled results indicated that gabapentin can decrease VAS score when compared to the control group with rest at 24 h in terms of VAS score (MD=-3.84; 95% CI -5.47 to -2.20; $P<0.001$, Figure 4).

A total of ten component studies (683 patients) perform data about VAS scores with rest at 48 h postoperatively. Meta-analysis result indicated that preoperative administration gabapentin

can decrease VAS score at 48 h postoperatively (MD=-1.98; 95% CI -3.55 to -0.40; $P=0.014$, Figure 4).

To test whether there is publication bias between the studies in terms of VAS score with rest at 24 h or 48 h postoperatively. Funnel plot results shows that studies at two flanks of ordinate is symmetry, which means there is no publication

bias between the studies (Figure 5). Begg's test further identify there is no publication bias between the studies ($P=0.098$, Figure 6).

VAS score with mobilization: Four component studies (546 patients) provided VAS scores at 24 h with mobilization postoperatively. Pooled results indicated that preoperative administration gabapentin can decrease the VAS score with mobilization at 24 h postoperatively (MD=-8.85; 95% CI -11.55 to -6.15; $P<0.001$, Figure 7). Only four studies with 546 TKAs reported the VAS score with mobilization at 48 h postoperatively; results revealed that gabapentin can also decrease the VAS score with mobilization at 48 h postoperatively (MD=-2.35; 95% CI -4.40 to -0.29; $P=0.025$, Figure 7).

Morphine cumulative consumption by 24 h and 48 h: Meta-analysis results indicated that preoperative oral gabapentin can decrease the cumulative morphine consumption at 24 h (MD=-11.99; 95% CI -15.75 to -8.24; $P=0.000$, Figure 8). However, there is no statistically significance between the included studies in terms of cumulative morphine consumption at 48 h (MD=-7.79; 95% CI -17.75 to -7.95; $P=0.126$, Figure 8).

Active knee flexion at day 3 and day 4 after TKA

The pooled results indicated that gabapentin can increase the active knee flexion at day 3 (MD=4.55; 95% CI 4.08 to 5.02; $P<0.001$, Figure 9) and day 4 (MD=3.02; 95% CI 2.61 to 3.44; $P<0.001$, Figure 9).

Complications: Four studies paid close attention to postoperative dizziness for the gabapentin and control group. Poole meta-

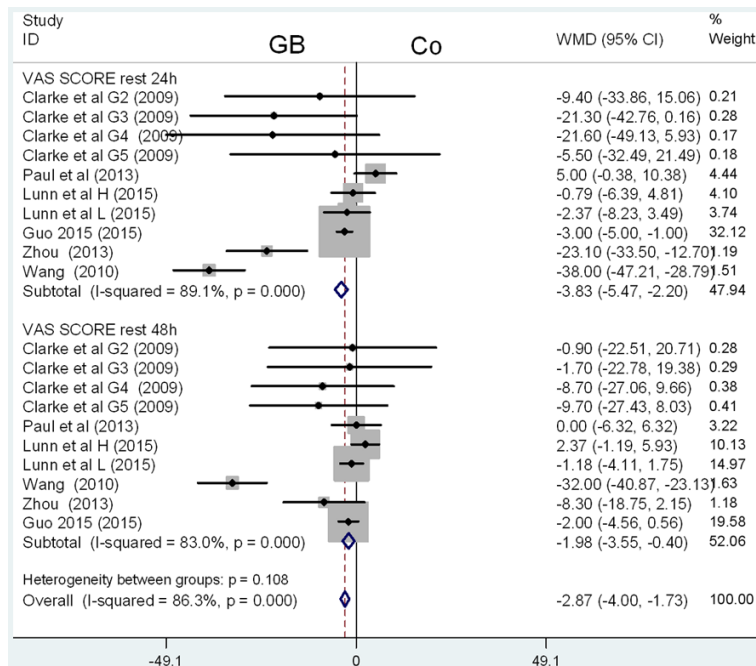


Figure 4. The forest plot of VAS score with rest at 24 h and 48 h.

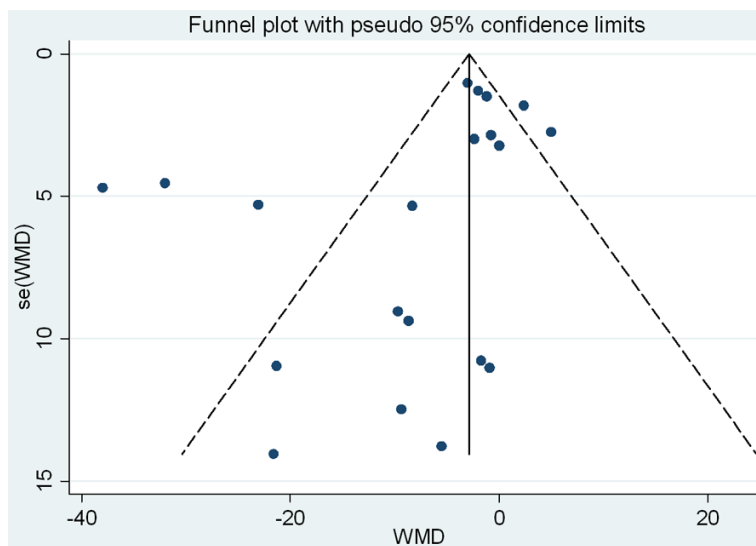


Figure 5. The funnel plot of VAS score with rest at 24 h and 48 h for each studies.

analysis indicated that gabapentin can decrease the occurrence of postoperative dizziness (RR, 0.66; 95% CI 0.48-0.92, $P=0.013$, **Figure 10**), with a large heterogeneity. Five studies investigated the occurrence of pruritus in both methods and found that the administration of gabapentin can decrease the occurrence of pruritus (RR, 0.41; 95% CI 0.31-0.55, $P=0.000$, **Figure 10**) and vomiting (RR, 0.56; 95% CI

0.37-0.86, $P=0.008$, **Figure 10**). There was no significant difference in terms of nausea and sedation (RR, 0.86; 95% CI 0.60-1.22, $P=0.571$, RR, 1.02; 95% CI 0.90-1.15, $P=0.793$, **Figure 10**).

Discussion

To our knowledge, this is the first meta-analysis of RCTs comparing the efficacy and safety of gabapentin with a placebo for the management of pain after TKA. The present meta-analysis was conducted on the basis of seven randomized studies that found better pain control with rest or mobilization at 24 h and 48 h postoperatively with gabapentin administration compared to controls. In addition, perioperative gabapentin administration can decrease the occurrence of dizziness and pruritus. Two articles were published in 2009; one was published in 2010, and the others were published from 2010. Five included studies were of high quality. The double-blind method was used in four RCTs and is unclear in two studies and is high bias at one RCT. All of the included studies presented comparable baseline data and provided sufficient data to be compiled.

The pain after TKA is typically severe and difficult to manage, early and effective pain relief especially important for early mobilization to decrease the length of the hospital stay and subsequent economic costs [17-19]. Multimodal postoperative analgesia has been recommended as to decrease severe pain with rapid onset, allow for early mobilization, provide good pain control and have minimal side effects after TKA. Gabapentin was first introduced as an antiepileptic drug in the year of 1993 and has since been used in many

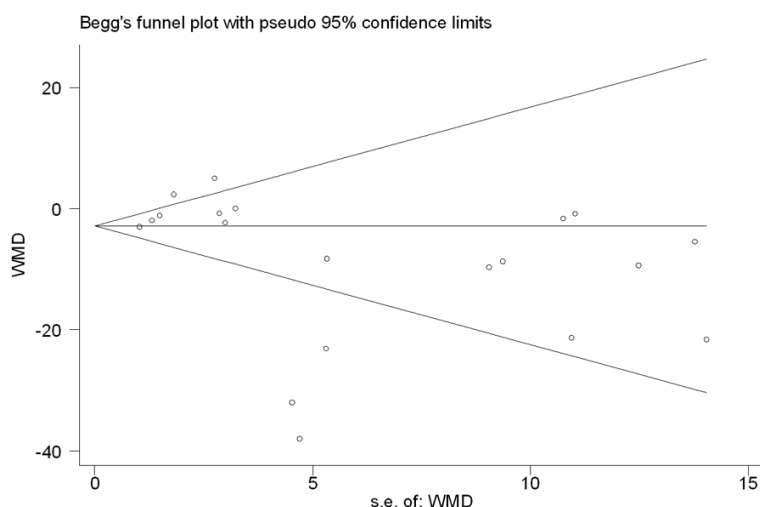


Figure 6. The Begg's test of VAS score with rest at 24 h and 48 h for each studies.

surgery fields. The effect of adjunct gabapentin on multimodal postoperative analgesia is controversial. Dahl et al [20] reported that there was no significant reduction in opioid consumption during the first 24 h in six of seven studies. Wiffen et al [21] reported that there is no role for gabapentin in the management of chronic and acute pain. Clarke et al [12] conducted a RCT and support that gabapentin can increase the knee function and reduce pain intensity after TKA.

The results of our meta-analysis indicated that gabapentin was effective in pain control with rest or mobilization at 24 h and 48 h postoperatively. There was no significant difference between the VAS score at 48 h with mobilization. Thus, more RCTs with VAS score at 48 h and even long-term follow up was needed to identify the effectiveness of gabapentin. The mechanism is gabapentin can decrease central nervous sensitization through in combination with the 21 subunits of presynaptic voltage-gated calcium channels. It has been demonstrated that the expression of these channels and calcium influx are up-regulated when nerve injury. Furthermore, gabapentin can decrease the hyper-excitability of secondary nociceptive neurons in the dorsal horn. This is in accordance with a study by Driks [22], who compared the effect of a single dose of gabapentin with a placebo on reducing postoperative pain after mastectomy with mobilization. Hwang et al [23] conducted a meta-analysis to compare the effect of gabapentin in the management of pain relief

after tonsillectomy and found that gabapentin provided pain relief without side effects. Zhai et al [24] conducted a meta-analysis based on RCTs and non-RCTs, the results indicated that gabapentin has no effect on VAS score with mobilization.

Pooled results indicated that gabapentin decreased the cumulative morphine consumption at 24 h and 48 h. This result concurs with previous study [25]; postoperative pain in patients managed with gabapentin can markedly reduces opioid consumption. Meanwhile, Doleman et al

[26] found that preoperative gabapentin can decrease the morphine consumption by a mean of 8.44 g after surgery. Paul et al [27] compare the effect of gabapentin on reducing morphine consumption at 72 h after total hip arthroplasty. Long-term follow up for observation gabapentin for cumulative morphine consumption is still needed.

Meta-analysis indicated that preoperative administration gabapentin can decrease the occurrence of morphine-related complications: pruritus, vomiting, nausea, sedation and dizziness. However, there was no significant difference in terms of vomiting, nausea and sedation between the two groups. In other fields, Grant et al [28] conducted a meta-analysis that comparing gabapentin for pain control in patients undergoing surgery and results indicated that gabapentin can decrease the morphine-related complications. So, preoperative gabapentin should be considered not only as part of a multimodal approach to postoperative analgesia, but also for prevention of PONV.

There were several limitations in this meta-analysis: (1) the dose and timing of gabapentin is differed between the included studies, moreover, the perioperative multimodal anesthesia was uniform, all of the perioperative pain management will affect the final results; (2) the duration of follow-up in some studies was unclear and not long enough, which might affect the final outcome; (3) though there is no publication bias in the meta-analysis, the pa-

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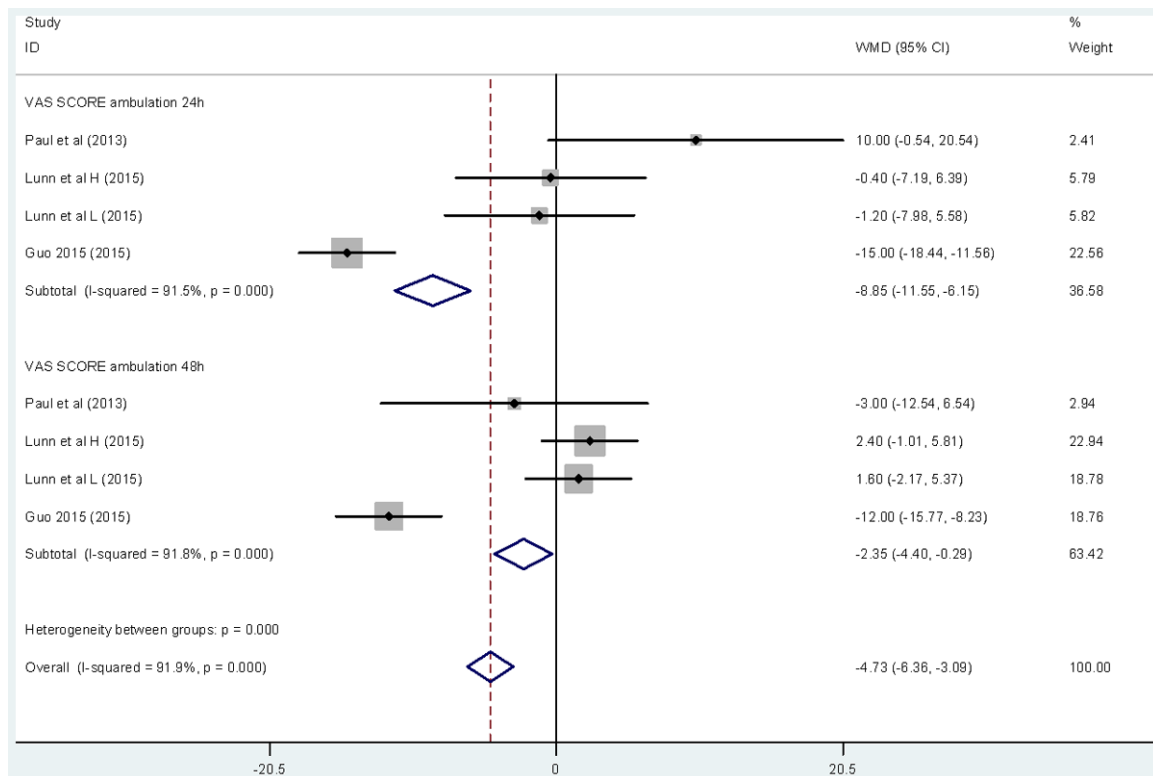


Figure 7. The forest plot of VAS score with ambulation at 24 h and 48 h postoperatively.

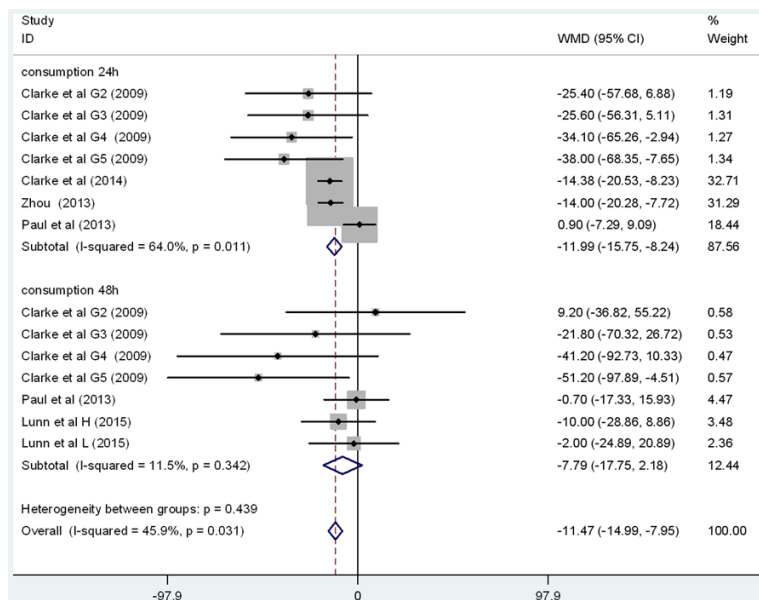


Figure 8. The forest plot about the effect of gabapentin on the cumulative morphine consumption at 24 h and 48 h.

tients in different countries may have selective bias and (4) seven RCTs with small sample

optimal dosing and timing of gabapentin in for reducing pain after TKA.

sizes, which may have caused imprecise outcomes.

Conclusion

In conclusion, although the number of studies and samples in each paper is limited, this is the first meta-analysis that compares the administration of gabapentin for the management of pain after TKA. Based on current meta-analysis, gabapentin has an analgesic and opioid-sparing effect in acute postoperative pain management without increasing the rate of dizziness and pruritus. However, the sample size and number of included studies is limited, a multiple central RCTs are still needed to identify the

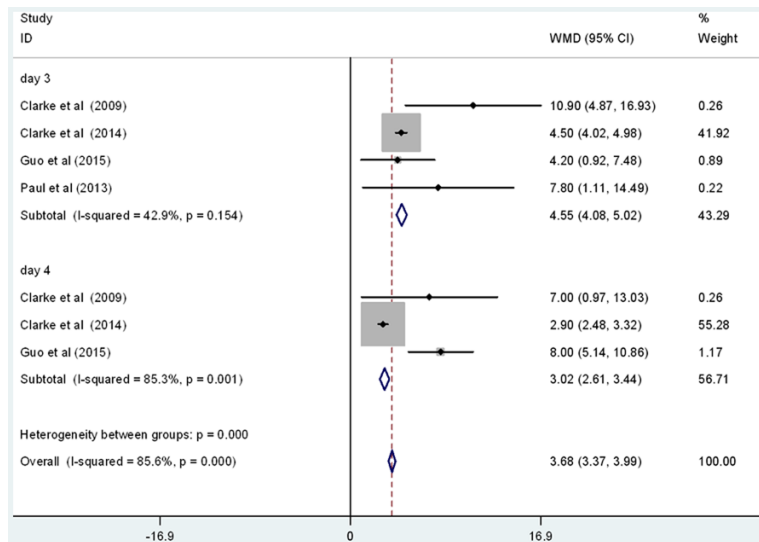


Figure 9. The forest plot comparing the active knee flexion of gabapentin versus control group.

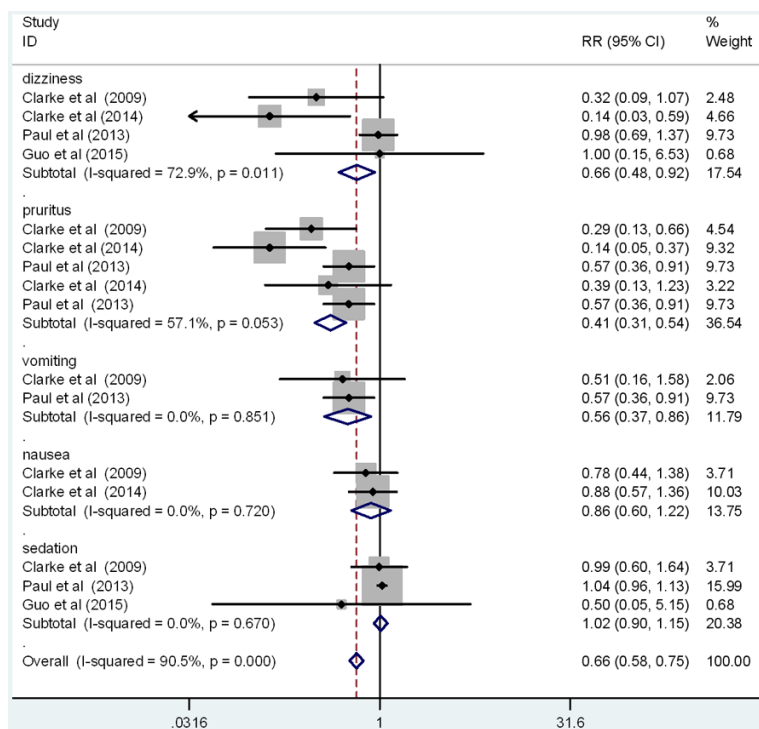


Figure 10. The forest plot about the occurrence of gabapentin on the dizziness, pruritus, vomiting, nausea and sedation.

Disclosure of conflict of interest

None.

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