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Is pregabalin effective and safe in total knee arthroplasty? A PRISMA-compliant meta-analysis of randomized-controlled trials

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Abstract

Background: Pain management after total knee arthroplasty (TKA) varies and has been investigated for years. Pregabalin as an anticonvulsant agent that selectively affects the nociceptive process has been used for pain relief after operation. This meta-analysis was conducted to examine the evidence of pregabalin in TKA.

Methods: Systematic searches of all related literatures were conducted using the following databases: MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials. Only randomized-controlled trials (RCTs) for TKA were included. The postoperative narcotic requirements, visual analog scale scores, knee flexion range, and relative risk of incidence rate of adverse effects in the pregabalin group versus placebo group were extracted throughout the study.

Results: Seven placebo-controlled RCTs met the inclusion criteria. The use of pregabalin significantly decrease the postoperative total morphine consumption ($P < .05$) and increase the passive knee flexion range ($P < .05$). Compared with the control group, the incidence of some side effects (nausea, vomiting, pruritus, and constipation) was less in the pregabalin group ($P < .05$).

Conclusions: The administration of pregabalin is not only efficacious in the reduction of narcotic requirements and incidence of some adverse effect, but also workable for the improvement of passive knee flexion range after TKA.

Abbreviations: CI = confidence interval, MD = mean difference, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCT = randomized-controlled trial, TKA = total knee arthroplasty, VAS = visual analog scale.

Keywords: arthroplasty, knee, meta-analysis, pregabalin

1. Introduction

Total knee arthroplasty (TKA) is a common operation in modern medicine, but it is particularly prone to postoperative pain with large surgical incision and relatively long operation times.[1] Trying to improve the surgical techniques and perioperative period management may be a good approach to ease pain, but the majority of patients undergoing TKA still experience intense pain after the operation. Many postoperative complications such as hypostatic pneumonia and deep venous thrombosis may associate with pain, they cannot only increase the treatment costs of patients, but also prolong the period of hospitalization.[2] Under such circumstances, the appropriate management to alleviate the postoperative pain plays a vital role in clinical practice.[3]

The postoperative pain score, the narcotic requirement, and the incidence of adverse effect were often used to evaluate the effect of multimodal analgesia.[4] Patients may develop intractable postoperative pain, even the multimodal approach had been provided.[5,6] Considering the various adverse effects of opioid analgesics, the use of some nonopioid agent, such as pregabalin, is often recommended.[7] As a 3rd-generation anticonvulsant agents, pregabalin can selectively affects the nociceptive process by inhibiting calcium influx via voltage-gated calcium channels.[8] It not only played the key role in both central and peripheral analgesia, but also relatively well-tolerated.[9]

In the past decades, some studies were conducted to evaluate the effects of pre-emptive pregabalin before the operation.[10–12] Although some conclusions had been made, the role of pregabalin alone in postoperative pain relief after TKA has rarely been investigated through a meta-analysis. The purpose of the present work is to evaluate the effect of the pregabalin from randomized-controlled trials (RCTs) and make a further exploration of the efficacy and safety of pregabalin in the reduction of postoperative pain and side effects in TKA.

2. Methods

This meta-analysis followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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CH and M-JK have contributed equally to this work.

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

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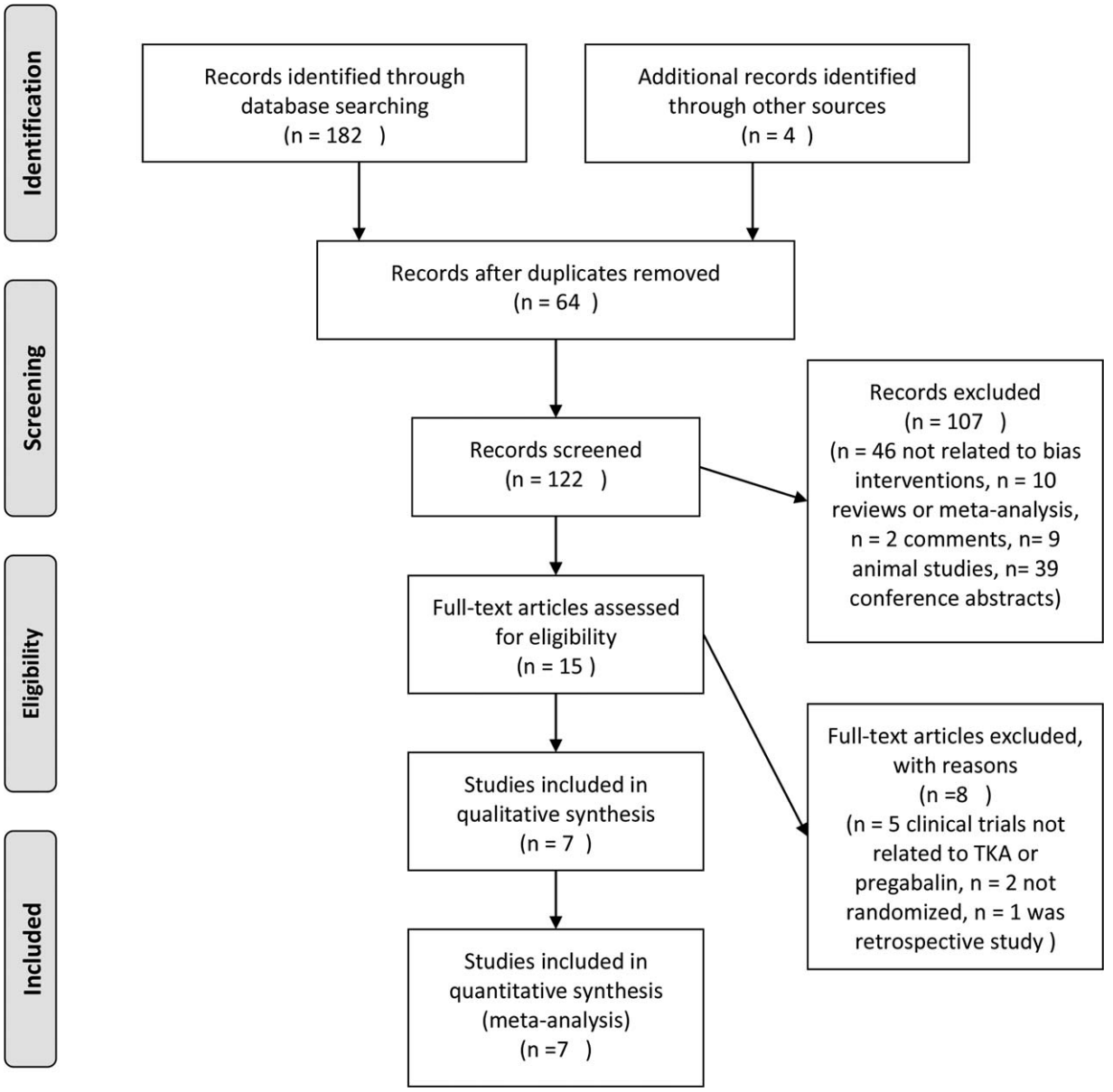

Figure 1. The selection of literature for included studies.

(PRISMA) statement.[13] Because this was a meta-analysis of former published literatures, ethical approval was not required. All literatures identified from different electronic-based search, including MEDLINE (1966 to present), EMBASE (1966 to present), and Cochrane Central Register of Controlled Trials. The following keywords combined with MeSH terms, and their combinations were used to maximize the search accuracy: "pain management, postoperative pain, TKA, total knee arthroplasty, total knee replacement, total joint arthroplasty, and pregabalin." The search was limited to RCTs in humans up to June 2016 (PRISMA Flow Diagram; Fig. 1).

2.1. Inclusion criteria

Literatures were regarded eligible for inclusion if the following criteria were fulfilled. Types of studies: RCTs with placebo, report in English. Population: Patients with unilateral TKA only. Types of interventions: pregabalin and placebo. Types of outcomes: at least one of the following items was reported: cumulative consumption of morphine, visual analogue scale (VAS) score, knee flexion range, and adverse effects.

2.2. Exclusive criteria

Patients were excluded from this work if they had bone neoplasms, serious osteoporosis, infection, metal sensitivity, or mental diseases.

2.3. Selection criteria

An eligibility assessment was carried out independently by 2 reviewers. Disagreements between reviewers were settled by discussion; if there was no consensus could be made, the third reviewer made the final decision as the adjudicator. The risk of

bias was assessed according the Cochrane Collaboration's tool, and the quality of the RCTs was evaluated by funnel plots.[14]

2.4. Data extraction

Data from the included studies were pooled by 2 authors (CH and M-JK) independently. The following data were extracted and analyzed: first author's name; publication year, number of patients, type of TKA, pregabalin regimen and dose, types and methods of narcotics, pain assessment methods, and adverse reactions. In studies in which data were unclear or incomplete, attempts were made to contact the authors for the missing data.

2.5. Statistical analysis

RevMan5.3 was conducted to analyze the pooled data (The Cochrane Collaboration, Oxford, UK). By the usage of chi-squared test, heterogeneity was evaluated by the value of P and I^2. $P > .10$ and $I^2 < 50\%$ were defined as having no significant heterogeneity. Then, a fixed-effects model was applied for data analysis. A random-effects model was used when the significant heterogeneity was found. For continuous outcomes, such as VAS scores and narcotic consumption, the mean difference (MD), and 95% confidence intervals (CIs) were pooled to express the results. Relative risk with 95% CIs was calculated for dichotomous data, such as vomiting, nausea, and other side effects. $P < .05$ was considered statistically significant.

3. Results

3.1. Literature search

A total of 186 potential records were identified with the electronic-based search, including 64 duplicated articles. By the assessment of the titles, and reading the abstracts, 115 articles were excluded as irrelevant, leaving 7 studies that eventually fulfilled the eligibility criteria.[15–21] The 7 placebo-controlled RCTs consisted of 479 patients in the pregabalin group and 483 patients in the control group. The publication time was between the years of 2010 and 2015. In all pooled literatures, "Singla 2015 (150 mg)" and "Singla 2015 (300 mg)" were the same trial, we divided this trial into 2 different dose comparisons (150 mg pregabalin vs. placebo; 300 mg pregabalin vs. placebo). "YaDeau 2015 (50 mg)," "YaDeau 2015 (100 mg)," and "YaDeau 2015 (150 mg)" were also belonged to 1 study, we divided this study into 3 different dose comparisons (50 mg pregabalin vs. placebo; 100 mg pregabalin vs. placebo; and 150 mg pregabalin vs. placebo).

3.2. Study characteristics

The key characteristics of the included pregabalin studies were illustrated in Table 1. All the relevant literatures were relatively small sample sizes, from 16 to 120 patients. The statistically characteristics were extracted from 2 groups.

3.3. Risk of bias assessment

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

3.4. Outcomes for meta-analysis

3.4.1. Postoperative narcotic requirements at 24 and 48 h.

Seven trials reported the details of postoperative narcotic consumption.[17,19–21] The pooled results from the meta-analysis showed a positive, the effect of pregabalin in all trials, significantly reducing postoperative narcotic consumption at 24 h (MD = −3.27, 95% CI: −6.05 to −0.49, $P < .00$; Fig. 3) and 48 h (MD = −9.11, 95% CI: −14.94 to −3.28, $P = .002$; Fig. 4). However, significant heterogeneity was found in 48 h ($\chi^2 = 32.49$, df = 6, $I^2 = 82\%$, $P < .00$).

3.4.2. Passive knee flexion range at 48 h. Four trials evaluate the passive knee flexion range.[15,18,20] Significant heterogeneity was found ($\chi^2 = 90.24$, df = 3, $I^2 = 97\%$, $P < .00$); therefore, a random model was performed. Compared with placebo, pregabalin could significantly increase postoperative passive knee flexion range at 48 h (MD = 3.87, 95% CI: 0.63–7.10, $P = .02$; Fig. 5).

3.4.3. Postoperative VAS at 24 and 48 h. Details regarding postoperative VAS were available in 7 trials[16–19,21] and 3

Table 1

Characteristics of included studies.

	Pregabalin/placebo										
				ASA grade (cases)							
Clinical trials	Cases	Age (mean)	Gender (% male)	I	II	III	Anesthesia	Dose, mg	Time of administration	Reference type	Location
Buvanendran 2010	120/120	64/63.3	24/30	N/A	N/A	N/A	Spinal anesthesia	300	1–2 h preoperatively	RCT	The United States
Buvanendran 2012	16/16	65/66	44/19	N/A	N/A	N/A	Spinal anesthesia	150	1 h preoperatively	RCT	The United States
Jain 2012	20/20	59.7/57.1	45/25	5/4	15/16	N/A	Spinal anesthesia	150	2 h preoperatively	RCT	India
Lee 2015	21/20	63.4/67.6	N/A	N/A	N/A	N/A	General anesthesia	150	1 h preoperatively	RCT	Korea
Niruthisard 2013	25/27	69/67	8/7	N/A	N/A	N/A	Spinal anesthesia	300	1 h preoperatively	RCT	Thailand
Singla 2015 (150 mg)	98/98	64/63	39/49	N/A	N/A	N/A	Spinal or epidural anesthesia	150	12 and 2 h preoperatively	RCT	The United States
Singla 2015 (300 mg)	96/98	63/63	37/49	N/A	N/A	N/A	Spinal or epidural anesthesia	300	12 and 2 h preoperatively	RCT	The United States
YaDeau 2015 (50 mg)	26/28	67/66	40/53	1/0	20/26	9/4	Epidural analgesia combined with femoral nerve block	50	30 min preoperatively	RCT	The United States
YaDeau 2015 (100 mg)	29/28	65/66	57/53	2/0	23/26	5/4	Epidural analgesia combined with femoral nerve block	100	30 min preoperatively	RCT	The United States
YaDeau 2015 (150 mg)	28/28	68/66	23/53	1/0	22/26	7/4	Epidural analgesia combined with femoral nerve block	150	30 min preoperatively	RCT	The United States

ASA = american society of anesthesiologists, RCT = randomised-controlled trial.

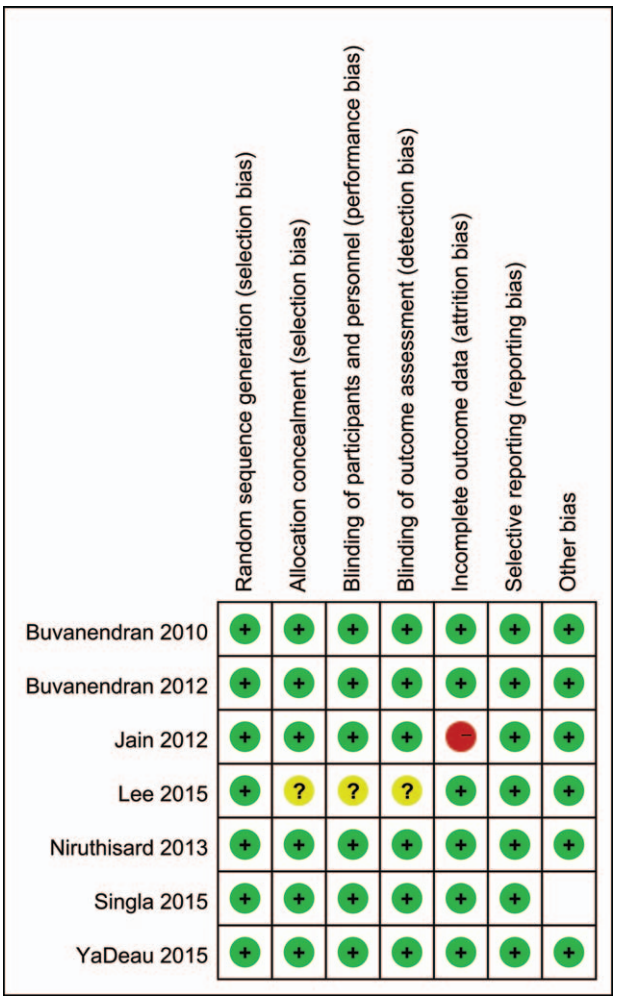

Figure 2. The bias risk of all trials.

trials,[17–19] respectively. Significant heterogeneity was found ($\chi^2=23.24$, df=6, $I^2=74\%$, $P<.00$; $\chi^2=13.79$, df=2, $I^2=76\%$, $P<.00$); therefore, a random model was performed. The result showed that no significant difference was found in the pregabalin groups compared with the control group at 24 and 48 h postoperatively (SMD=−0.20, 95% CI: −0.64 to 0.23, $P=.36$; Fig. 6; SMD=−0.50, 95% CI: −1.44 to 0.44, $P=.30$; Fig. 6).

3.4.4. Adverse effects. Eight studies reported the incidence rate of nausea, which was the most common adverse effect in the included trials.[15,17,18,20,21] Significant heterogeneity was not found in the included studies; therefore, a fixed model was used ($\chi^2=9.52$, df=7, $I^2=27\%$, $P=.22$). Compared with placebo, pregabalin could significantly reduce the incidence rate of nausea postoperatively (relative rate 0.71, 95% CI: 0.59–0.86, $P<.00$; Fig. 7).

The second-most reported side effect was pruritus, 5 studies record the incidence rate of pruritus.[15,17,18,20] No significant heterogeneity was found; therefore, a fixed model was used ($\chi^2=1.28$, df=4, $I^2=0\%$, $P=.87$). Compared with the placebo group, the incidence rate of pruritus was less in the pregabalin groups (relative rate 0.65, 95% CI: 0.44–0.98, $P=.04$; Fig. 8).

Four studies reported the incidence rate of vomiting.[15,17,20] No significant heterogeneity was found, a fixed model was applied ($\chi^2=2.33$, df=3, $I^2=0\%$, $P=.51$). Compared with the control group, pregabalin could significantly decrease the incidence rate of vomiting (relative rate 0.54, 95% CI: 0.37–0.78, $P=.001$; Fig. 9).

Three studies showed the incidence rate of constipation.[17,20] Significant heterogeneity was not shown between pooling results; therefore, a fixed model was applied ($\chi^2=3.54$, df=2, $I^2=43\%$, $P=.17$). Compared with the control group, pregabalin could significantly decrease the incidence rate of constipation as well (relative rate 0.63, 95% CI: 0.45–0.89, $P=.009$; Fig. 10).

Five studies reported the incidence rate of somnolence.[20,21] Significant heterogeneity was not found; therefore, a fixed model was applied ($\chi^2=1.88$, df=4, $I^2=0\%$, $P=.76$). Compared with the control group, somnolence was more found in the pregabalin groups (relative rate 1.29, 95% CI: 1.00–1.68, $P=.05$; Fig. 11).

Five studies reported the incidence rate of dizziness.[15,17,18,20] Significant heterogeneity was not found, a fixed model was used ($\chi^2=1.95$, df=4, $I^2=0\%$, $P=.74$). Compared with the control group, the incidence rate of dizziness was more in the pregabalin group (relative rate 1.46, 95% CI: 1.04–2.06, $P=.03$; Fig. 12).

Five studies reported the incidence rate of confusion.[15,20,21] Significant heterogeneity was not found; therefore, a fixed model was applied ($\chi^2=0.99$, df=4, $I^2=0\%$, $P=.91$). Compared with the control group, confusion was more found in the pregabalin groups (relative rate 2.44, 95% CI: 1.36–4.38, $P=.003$; Fig. 13).

Three studies reported the incidence rates of headache,[15,20] peripheral edema,[15,20] and urinary retention,[17,20] respectively. Significant heterogeneity was not found in those studies, a fixed model was used ($\chi^2=3.73$, df=2, $I^2=46\%$, $P=.15$; Fig. 13; $\chi^2=0.29$, df=2, $I^2=0\%$, $P=.86$; Fig. 14; $\chi^2=0.27$, df=2, $I^2=0\%$,

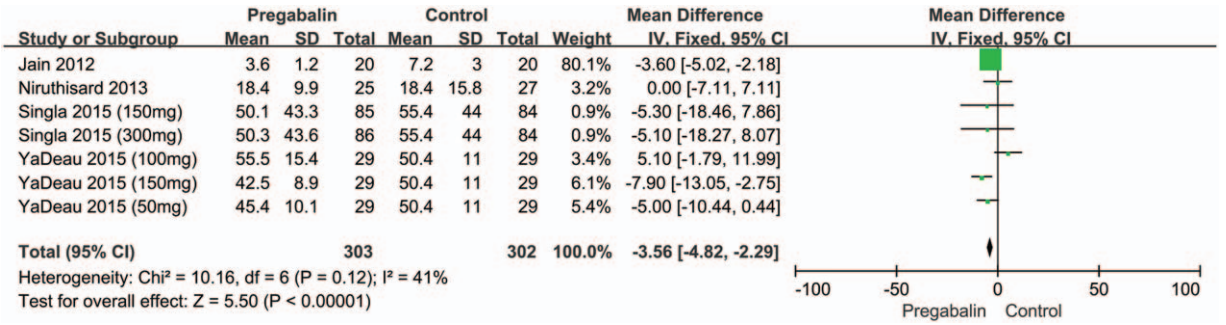

Figure 3. Forest plot of postoperative narcotic consumption at 24 h between the 2 groups.

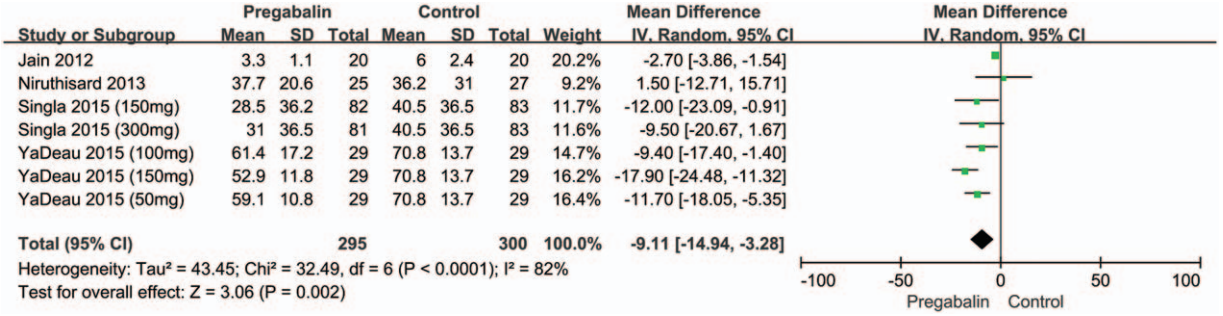

Figure 4. Forest plot of postoperative narcotic consumption at 48 h between the 2 groups.

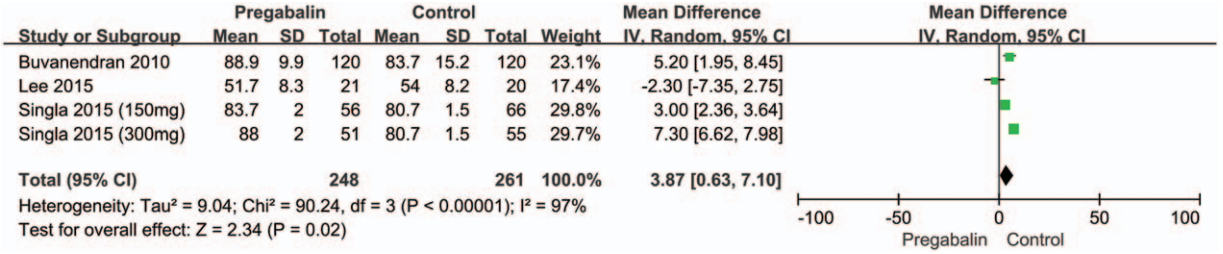

Figure 5. Forest plot of passive knee flexion range at 48 h between the 2 groups.

$P = .87$; Fig. 15). Compared with the control groups, no significant difference was found in pregabalin groups (relative rate 0.74, 95% CI: 0.37–1.46, $P = .38$; Fig. 14; relative rate 0.75, 95% CI: 0.42–1.36, $P = .35$; Fig. 15; relative rate 0.84, 95% CI: 0.37–1.90, $P = .68$; Fig. 16).

4. Discussion

Our meta-analysis of the pooled data directed to evaluate the relevant literatures systematically and create a profound understanding of the effectiveness and safety of pregabalin in the management of postoperative pain after TKA. Our overall results demonstrated that compared with the placebo, the administration of pregabalin could significant reduce the cumulative morphine consumption at 24 and 48 h postoperatively. This result was coincident with the former studies examining the effect of pregabalin in different surgical operation.[10–12,22,23]

Passive knee flexion range postoperatively is also a good indicator to assess the effect of TKA. Our work revealed that

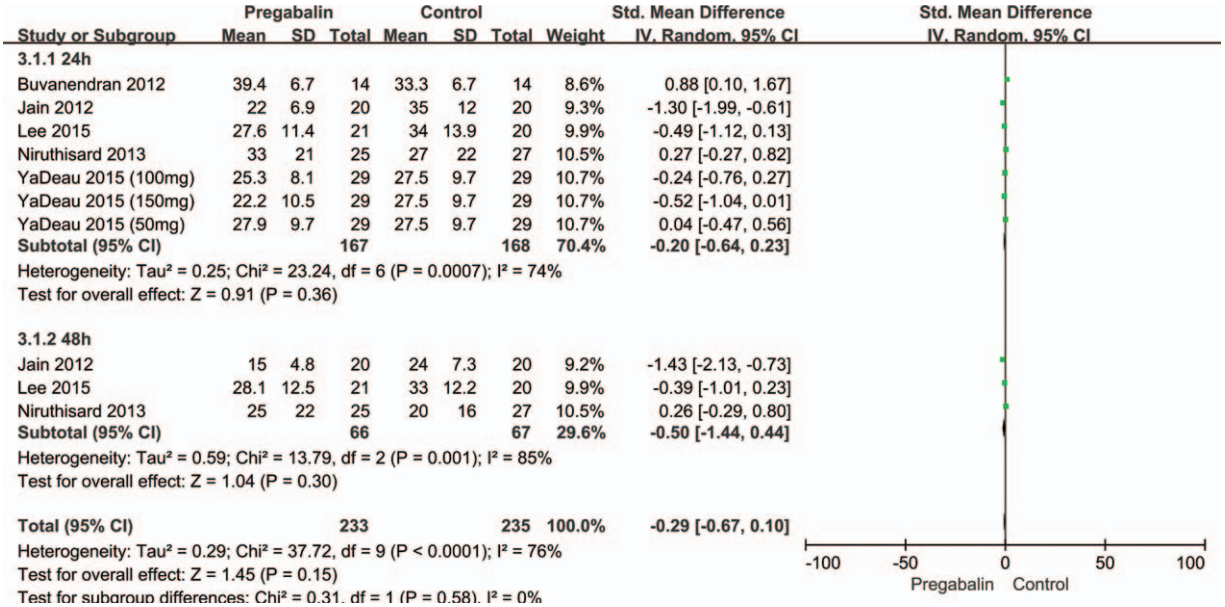

Figure 6. Forest plot of postoperative visual analog scale at 24 and 48 h between the 2 groups.

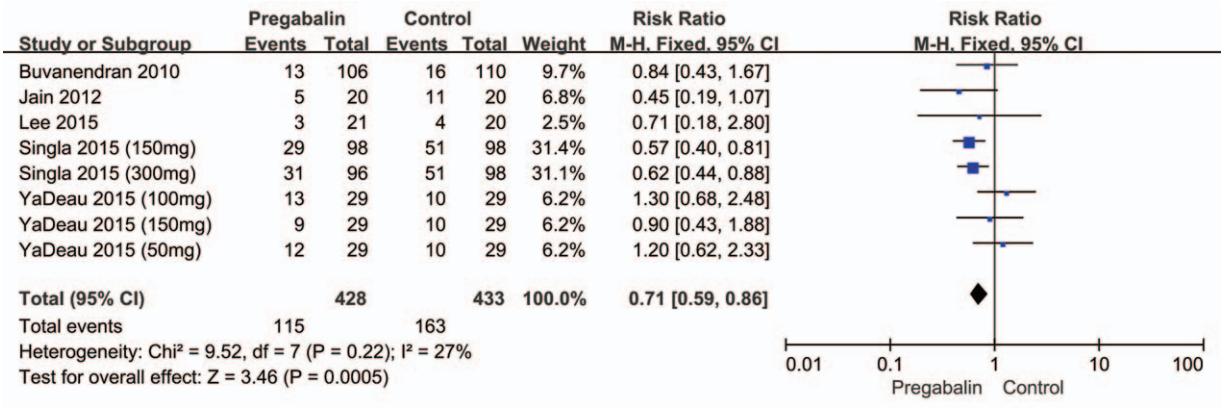

Figure 7. Forest plot of incidence of nausea between the 2 groups.

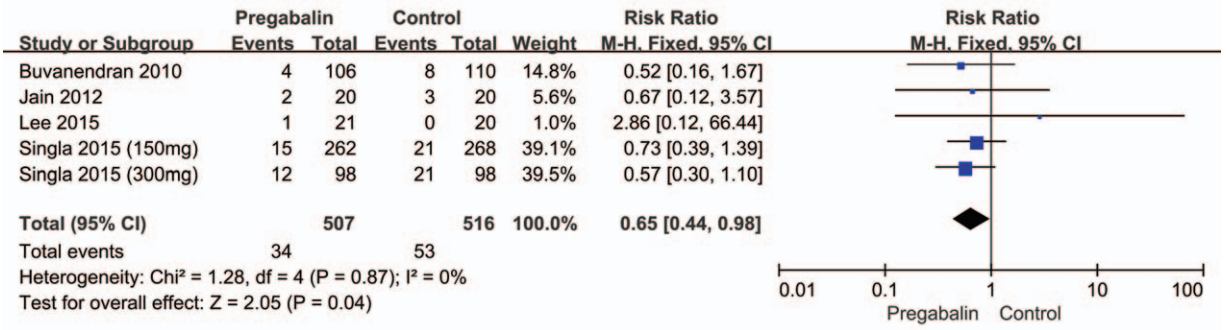

Figure 8. Forest plot of incidence of pruritus between the 2 groups.

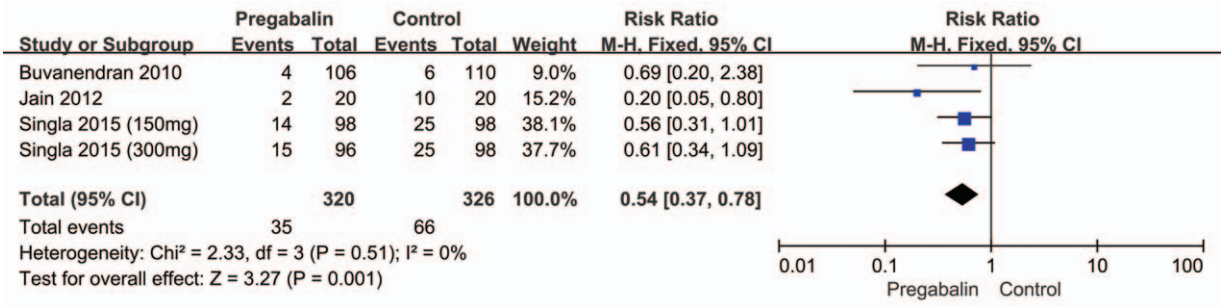

Figure 9. Forest plot of incidence of vomiting between the 2 groups.

Figure 10. Forest plot of incidence of constipation between the 2 groups.

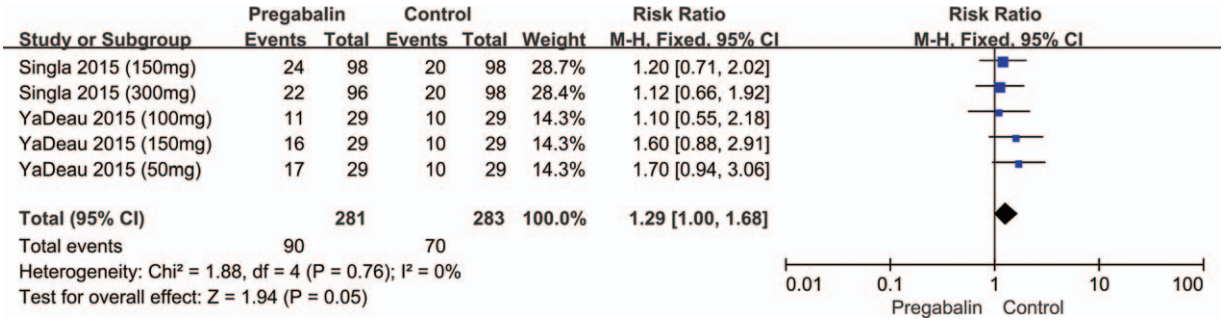

Figure 11. Forest plot of incidence of somnolence between the 2 groups.

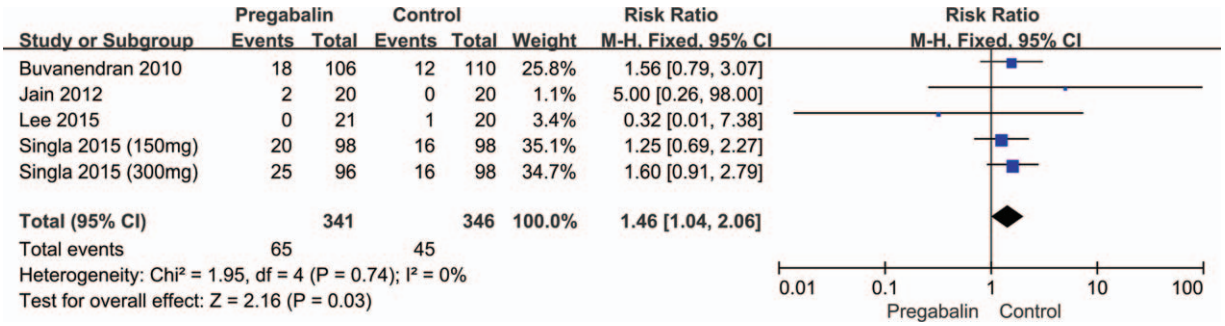

Figure 12. Forest plot of incidence of dizziness between the 2 groups.

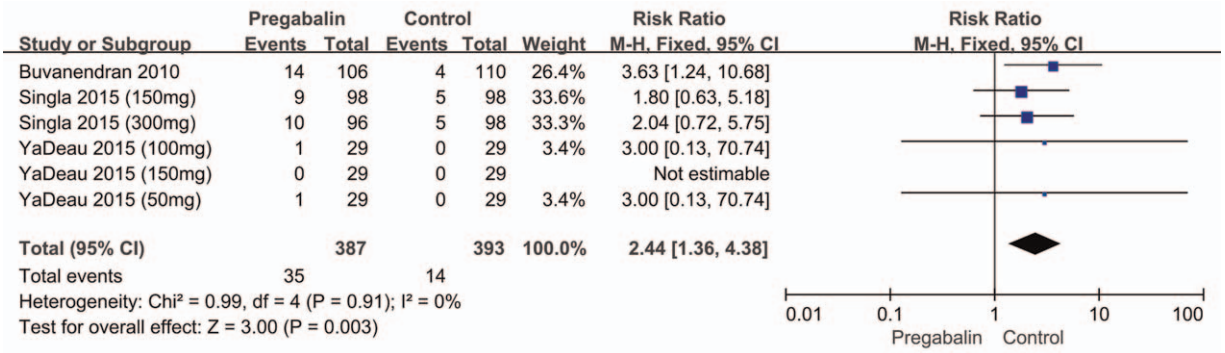

Figure 13. Forest plot of incidence of confusion between the 2 groups.

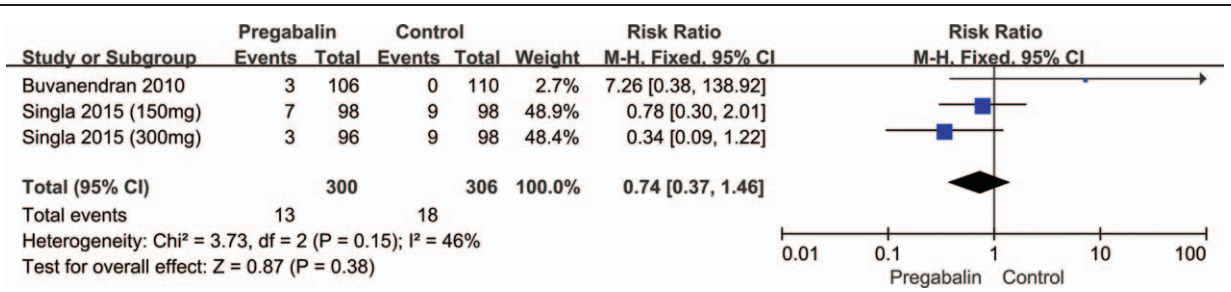

Figure 14. Forest plot of incidence of headache between the 2 groups.

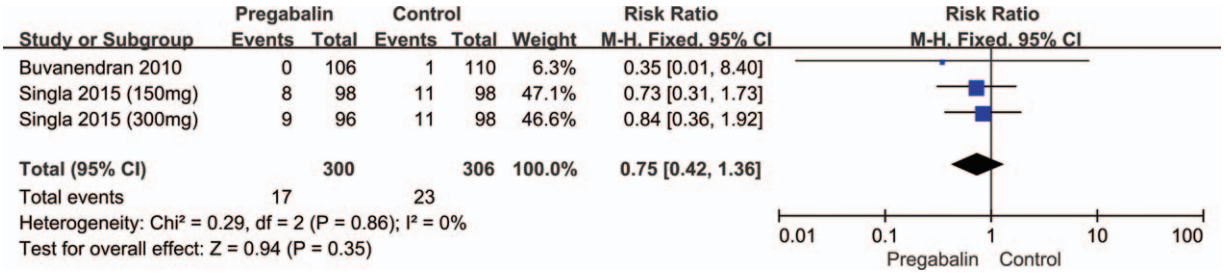

Figure 15. Forest plot of incidence of peripheral edema between the 2 groups.

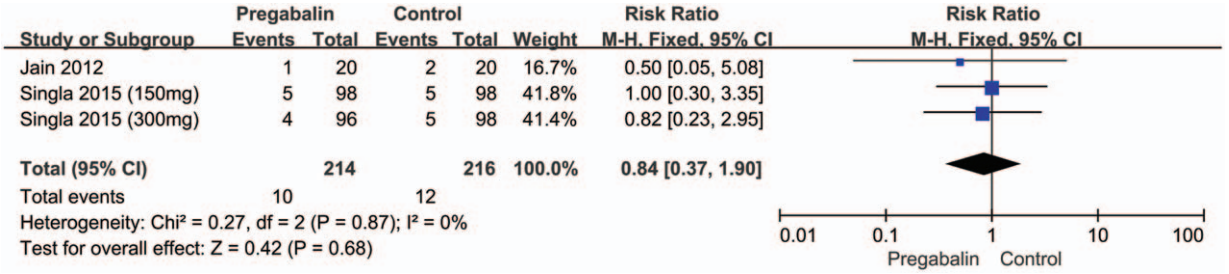

Figure 16. Forest plot of incidence of urinary retention between the 2 groups.

patients in the pregabalin group had greater passive flexion range at 48 h postoperatively compared with placebo patients. This could be associated with many aspects of operation. Only in good conditions, such as less incidence of side effects, can patients willing to do more excises of their operated legs. The improvement of flexion range have profound influences for reducing the therapy costs and time which was a key points for the better recovery of patients.[24]

In order to assessing the effect of pregabalin in relief of postoperative pain, the VAS scores were often employed in clinic. In this part, the postoperative VAS score at 24 and 48 h was used as the point of postoperative pain assessment. However, compared with the control group, the significant reductions in VAS score were not found at all time points in the pregabalin group. This finding of our research was consistent with those of previous studies as well.[25,26]

Nausea, pruritus, vomiting, and constipation were the common complications in the postoperative period when pregabalin was applied. As shown in Figs. 6 to 9, the incidence rates of those side effects appeared to increase significantly in the control group when compare with the pregabalin group. Previous researches reported that pregabalin administration is related to with decreased postoperative side effects,[7,27] our meta-analysis was in accordance with the former studies. Regarding other side effects, such as vomiting, dizziness, and confusion, we found that the incidence rates of them were significantly increased in the pregabalin group. This finding is interesting, many factors such as the different methods of anesthesia or opioid use might related to the final result; the variety of sample sizes and operating methods could also explain this discrepancy. Whether these side effects are dose-related still unknown.

As far as we know it, this meta-analysis might be the first one regarding pregabalin alone in the treatment of postoperative pain after TKA. In order to overcome the shortcomings of observational or retrospective studies, all of the included literatures were RCTs. However, due to the various study designs and the analytical approach, the heterogeneity in those studies may be occur. There are several potential limitations to our meta-analysis. For one thing, some influence factors, such as the type of TKA, duration of operation, and complications, may also play a vital role in the management of pain intensity; for another, the administration time and dosages of pregabalin were various: the dose range was from 50 to 300 mg and the administration time was 1 h preoperative in some trials and 2 h preoperative in others. However, our analysis demonstrated that the pregabalin had a significant effect on the cumulative narcotic consumption as well as passive knee flexion range in all time points. Akhavanakbari et al[27] found that a single preoperative oral dose of pregabalin 150 mg is effective for pain relief. However, Buvanendran et al[28] suggested that oral administration of 300 mg pregabalin could reach the sufficient central nervous system drug concentrations. It seems as if we can hardly claim that what the best dosages and time of pregabalin are from this work, further studies are needed to further investigate the best use of pregabalin.

At last, because almost all of the included literatures were conducted by anesthetists, some valuable information such as operative approach, types, and methods of internal fixation were not reported in many trails. However, it is believed that these information may be usually crucial points to the spine surgeons and have the large effect on degree of postoperative pain, so it is needed to take these factors into account in future studies.

5. Conclusion

This meta-analysis of RCTs studies reveals that pregabalin was efficacious in the reduction of postoperative narcotic requirements, passive knee flexion range, and incidence rate of some adverse effect after TKA.

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