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Original Article

Efficacy of perioperative celecoxib use in primary total knee and hip arthroplasty: a meta-analysis

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Abstract: Objective: Perioperative pain is a serious problem that interferes with postoperative rehabilitation and hospital stays. There is no definitive evidence regarding the analgesic efficacy of celecoxib. Therefore, we conducted a meta-analysis to estimate the efficacy and safety of celecoxib for patients after total hip arthroplasty (THA) and total knee arthroplasty (TKA). Method: Related articles were mainly searched from Medline, PubMed, Embase, the Cochrane Central Register of Controlled Trials, and Google Scholar. Keywords "TKA OR THA OR knee replacement OR hip replacement OR arthroplasty" AND "celecoxib" in combination with Boolean operators were used to extract the studies. We select RevMan 5.3 software to conduct the meta-analysis. Results: Six randomized controlled trials are included in our meta-analysis. There were significant differences in visual analogue scale, range of motion, and mean opioid consumption comparing the celecoxib group with placebo group after TKA. However, the differences in total blood loss and postoperative nausea and vomiting were not significant between the two groups. Conclusions: Celecoxib can decrease the postoperative pain and reduce opioid consumption, as well as increasing knee joint motion. The use of celecoxib is worthy of recommendation as a standard analgesic protocol for pain treatment after TKA and THA.

Keywords: Celecoxib, arthroplasty, meta-analysis

Introduction

Total knee arthroplasty (TKA) and total hip arthroplasty (THA) are preferred surgical approaches of knee joint arthritis [1, 2]. With the increase in population aging, patients who require TKA or THA treatment of arthritis has increased steadily in the past decades. This trend will continue in the foreseeable future [3]. However, there are no effective therapeutic options to deal with the considerable perioperative pain caused by a mass of soft tissue damage and bone destruction. Although most patients suffer from pain, appropriate pain management can reach early functional recovery [4].

Opioid analgesics are commonly used in clinical analgesic therapy, but adverse events, such as excessive sedation, respiratory depression, drug tolerance, urinary retention, vomiting, and nausea, remain a serious problem [5, 6]. Conventional nonsteroidal anti-inflammatory drugs (NSAIDs) play an important role in analgesia and anti-inflammation, which inhibit the cyclooxygenase (COX) enzyme to decrease the release of inflammatory factors. Traditional NSAIDs are nonselective inhibitors of COX, which has been divided into two different isoforms: COX-1 and COX-2 [7]. COX-1 is involved in routine physiological processes and defensive functions and mainly exists in blood vessel and kidney tissue. The COX-2 isoform is expressed in tissues after surgery and is associated with inflammatory reactions [7, 8].

Nonselective NSAIDs compromise the gastric mucosa, platelets, and kidneys, causing gastropathy, antiplatelet aggregation effects, and renal disease, respectively. Selective COX-2 inhibitors can effectively reduce these side effects. It is a good choice for perioperative use during postoperative pain management [9-12]. Celecoxib as a typical COX-2 inhibitor has a significant role in reducing opioid analgesic consumption and improving range of motion (ROM)

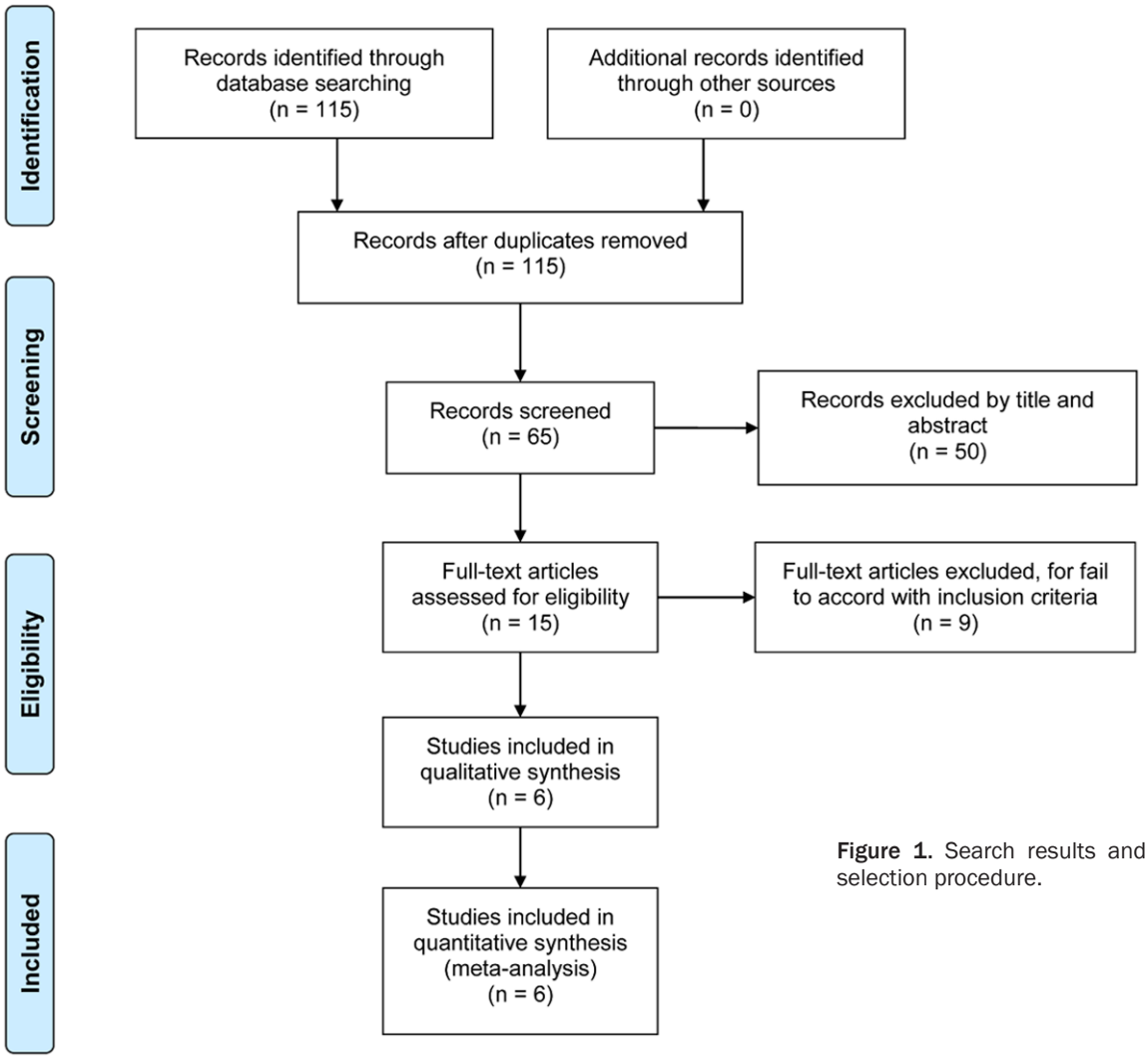

Figure 1. Search results and selection procedure.

Table 1. Cohort characteristics

Studies	Cases (C/P)	Mean Age (C/P)	Male patient (C/P)	Celecoxib dosage (mg)	Reference type	QAS
Schroer 2011	53/54	67/67	20/25	200	RCT	7
Meunier [1] 2007	25/25	69/68	14/8	200	RCT	7
Gong 2013	48/49	66/65	7/6	300	RCT	7
Huang 2008	40/40	70/70	N/A	200	RCT	6
Meunier [2] 2009	25/25	69/68	14/8	200	RCT	7
Ittichaikulthol 2010	40/40	64/68	8/11	400	RCT	6

C/P: celecoxib/placebo, N/A: not applicable, QAS: quality assessment score, RCT: randomized controlled trial.

after primary TKA [13]. Reducing opioid use provides clinical benefits for patients undergoing TKA and THA. Although a number of clinical studies have discussed the perioperative analgesic effect of celecoxib, there were still no definitive conclusions. However, celecoxib has a good analgesia effect on acute postoperative pain with high safety [14]. Consequently, we conducted a meta-analysis to collect information from randomized controlled trials (RCTs) and non-RCTs to clarify the perioperative analgesia effects of celecoxibuse in patients after primary TKA and THA.

Materials and method

Search strategy

Related RCT articles were mainly searched from Medline (1966-November 2015), PubMed (1980-November 2015), Embase (1980-November 2015), the Cochrane Central Register of Controlled Trials, and Google Scholar. According to the Cochrane Collaboration guide-

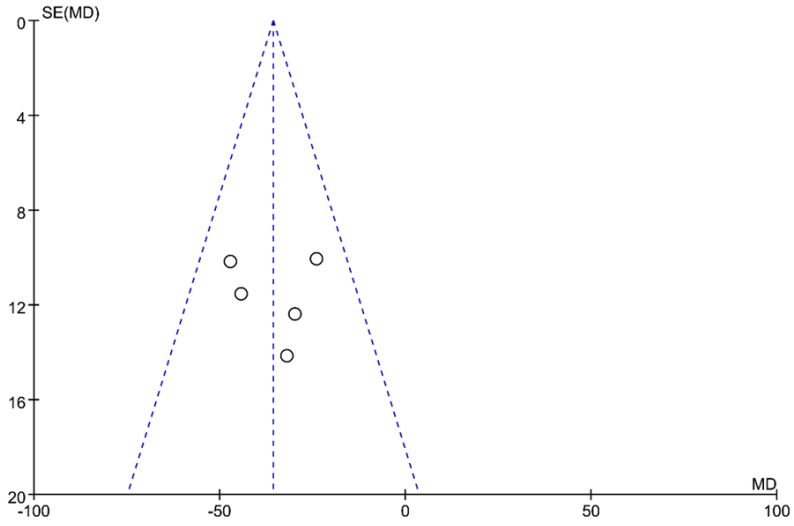

Figure 2. Funnel plot of opioid consumption.

lines, we also conducted other databases. To improve the sensitivity and specificity of searching, we used the keywords in combination with Boolean operators "AND" or "OR" as follows: "TKA OR knee replacement OR arthroplasty" AND "celecoxib". The search strategy is presented in **Figure 1**.

Inclusion criteria

Included studies were considered eligible if they met the following criteria:

Study design: Interventional or observational studies.

Population: Patients were scheduled for primary TKA and THA.

Intervention: Celecoxib

Comparator: Placebo or nothing.

Outcomes: Visual analogue scale (VAS), ROM, blood loss, morphine consumption, postoperative complications, physical composite score (PCS), knee society score (KSS), and physical functioning.

Exclusion criteria

Studies were excluded if the patients had a history of coagulopathy or of a thromboembolic event, malignant disease, acute infection, myocardial infarction, and unstable angina, allergy to NSAIDs, peptic ulcers, mental disorder, severe metabolic or endocrine disturbances, and severe renal or hepatic disease.

Quality assessment

We included all the RCTs published in an electronic database that were associated with celecoxib and control groups (placebo or nothing) in patients who underwent primary TKAs. Two reviewers (MJ. K. and JX. M.) screened the titles and abstracts independently. According to the Cochrane Handbook for Systematic Reviews of Interventions, the methodological quality and basis of the included literature were assessed as follows: (1) generation of random sequences, (2) randomization concealment, (3) blind method of participant and outcome assessment, and (4) excluding reasons.

Data extraction

Two of the authors (MJ. K. and JX. M.) extracted relevant data independently from eligible literature, with a standard data extraction form, including the title, first author of the study, year of publication, patient demographics, sample size, indications of TKA operation, numeric rating scale, ROM, blood loss, KSS, opioid consumption, postoperative complications, and incidence of side effects. If necessary, we contacted the corresponding authors of the included studies to ensure the information was integrated and to get any missing data. The pooled data were confirmed by XL. M.

Outcome

VAS, ROM, blood loss, and morphine consumption were primary outcomes. The secondary outcomes, such as postoperative complications, KSS, PCS, and deep vein thrombosis (DVT), were included. Other outcomes, such as physical functioning, emotional roles, Oxford knee score (OKS), sleep disturbance, and mental composite score (MCS), were also mentioned in some eligible studies.

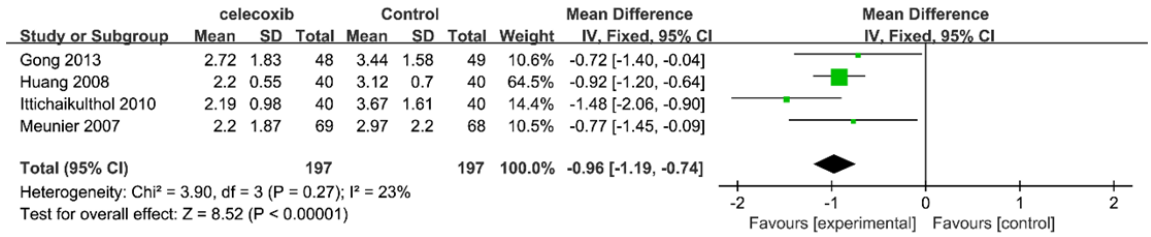

Figure 3. Effect of celecoxib illustrated by forest plot diagram on VAS at rest.

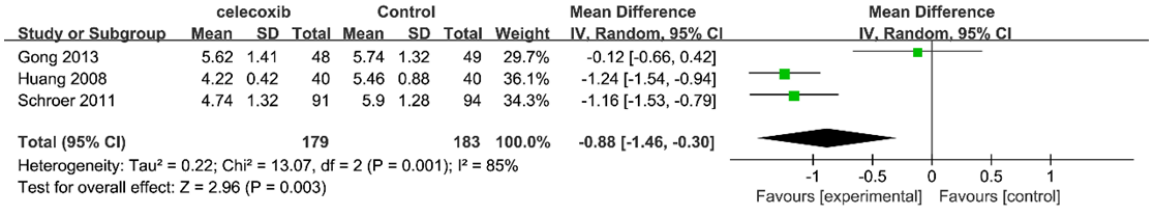

Figure 4. Effect of celecoxib illustrated by forest plot diagram with VAS on ambulation.

Table 2. Subgroup analysis of VAS pain scores on ambulation

Subgroup	Studies	Effect estimate				
		χ^2	I^2 (%)	MD	95% CI	*P* value
Tourniquet apply	2	13.7	93	-0.68	-1.69, 0.34	0.19
Celecoxib does (200 mg)	2	0.25	0	-1.17	-1.25, -1.08	0.00001
One surgeon performed TKA	2	12.45	92	-0.7	-1.08, 0.39	0.21

Data analysis and statistical methods

Review Manager Software for Windows (Version 5.3. Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014) was used to present study findings and combine the estimated effect of treatments. Statistical heterogeneity of the included studies was conducted by Q and chi-square test in accordance with the values of *P* and I^2. A fixed-effects model was used if the I^2<50% and P>0.1. Otherwise, we believed that the data had high heterogeneity, and a random-effects model was used. For continuous outcomes, mean differences (MDs) and 95% confidence intervals (CIs) were used to weigh the effect size. Relative risks (RRs) and 95% CIs were used for the dichotomous outcomes. The inverse variance and Mantel Haenszel techniques were used to combine separate statistics. *P* values <0.05 were considered to be statistically significant.

Results

Search result

A total of 115 relevant articles were identified according to the search strategy and abstracts. Six RCTs [13, 15-19] were included by reading the abstract and entire article in detail. Eventually, 464 patients were enrolled for data extraction and meta-analysis at a final follow-up. Preoperative demographics and baseline of patient characteristics are illustrated in **Table 1**. The sample sizes of the eligible articles ranged from 50 to 107. The modified Jadad scale [20] was used to evaluate the quality of the RCTs. All of the patients reported in the six RCTs were randomly numbered. Four RCTs [13, 15, 17, 19] had both patients and observers blinded to the methods for the study. Huang [16] used an observer-blind study design. The exclusion criteria were applied among all RCTs to decrease the biases of patient selection. Gong [13], Huang [16], and Schroer [17] mentioned the TKA surgeries were operated by the same surgeon. All articles except Meunier [15] reported the pre-operation VAS and ROM as a comparison with post-operation. VAS pain scores on rest were performed in five studies

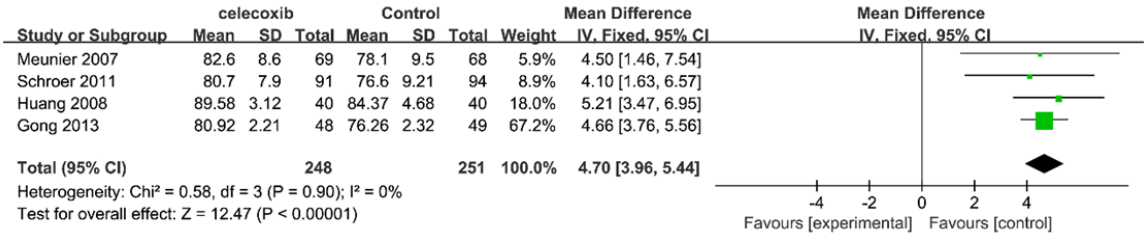

Figure 5. Effect of celecoxib illustrated by forest plot diagram on ROM.

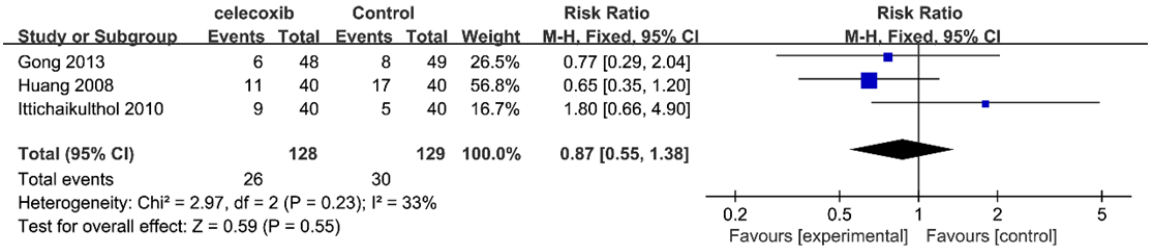

Figure 6. Effect of celecoxib illustrated by forest plot diagram on PONV.

[13, 15-19] to measure the immobilization conditions of patients. Schroer [17], Gong [13], and Huang [16] recorded the VAS pain scores on ambulation to investigate the movement ability of knee joints. ROM was presented in four RCTs [13, 15-17] by the doctor to measure the movement range of knee joints. Total blood loss was mentioned in four RCTs articles, but only Meunier [15] and Gong [13] provided the male and female blood loss separately. All five studies reported the opioids consumption; nevertheless, different units of measurement were used to record opioid consumption. We converted opioid use in all articles to morphine equivalents (Meq) with the following formula: 1/3 [mg PO morphine] + 1/2 [mg PO oxycodone] + 1/3 [mg PO hydrocodone] + 1/20 [mg PO codeine] + 10/7.5 [mg PO hydromorphone] + [mg IV morphine] + 10/1.5 [mg IV hydromorphone] + 1/10 [mcg IV fentanyl] [21]. Postoperative complications, such as nausea and vomiting, were presented in three studies [13, 16, 18], according to the nursing records. Schroer [17] and Meunier [15] mentioned a 1-year follow-up. Gong [13] and Huang [16] showed that their follow-up period was limited to an early stage after operation (less than 7 days). Meunier [19] reported a 2-year follow-up of VAS and ROM in TKA and THA patients. Because of length of stay and time of follow-up were different in the six articles, we chose the data less than a week as a short-term indicator among primary TKA and THA patients to extract data. Surgery time was also recorded in six RCTs. Only Huang [16] provided the data of tourniquet duration, which is used to reduce the amount of bleeding through compressing the lower limbs during the surgery.

Publication bias was also evaluated using a funnel plot diagram (**Figure 2**). The diagram was symmetrical, indicating low risk of publication bias.

Results

VAS scores at rest (24 h)

The VAS scores with rest at 24 hours was reported in four studies [13, 15, 16, 18]. The data indicated that the celecoxib group was more effective than the placebo group in reducing the pain at rest. The difference was significant according to the data pooled from **Figure 3** in TKA and THA patients (MD = -0.96, 95% CI: [-1.91, -0.74], P<0.00001). Because statistical heterogeneity was not found in four included studies (χ^2 = 3.90, df = 3, P = 0.27, I^2 = 23%), a fixed model was applied in this study.

VAS scores on ambulation (72 h)

Three studies [13, 16, 17] reported the VAS pain scores on ambulation at 72 hours. The data (MD = -0.88, 95% CI: [-1.46, -0.30], P =

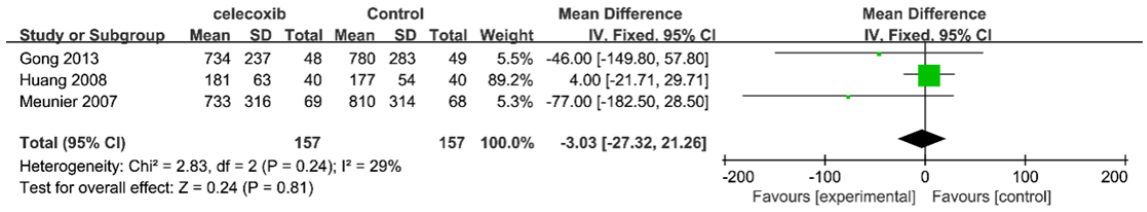

Figure 7. Effect of celecoxib illustrated by forest plot diagram on total blood loss.

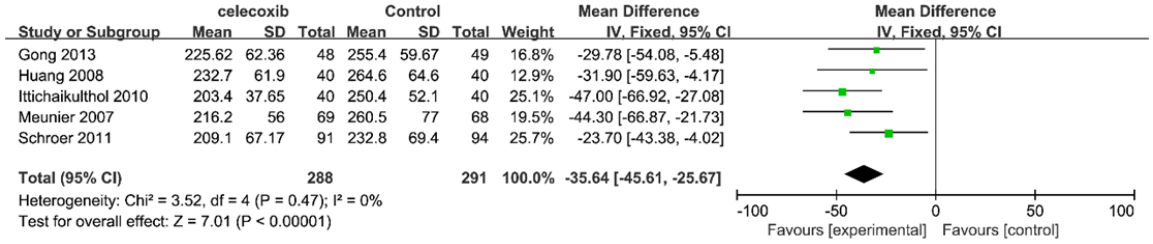

Figure 8. The effect of celecoxib illustrated by forest plot diagram on mean opioid consumption.

0.003, **Figure 4**) showed a significant difference, which indicated that celecoxib was a useful drug for decreasing postoperative pain after TKA with a short time for ambulation. A significant heterogeneity was shown in this study (χ^2 = 13.07, df = 2, P = 0.001, I^2 = 85%); therefore, a random-effects model was used. Subgroup analysis and sensitivity analysis were executed to analyze the reasons of heterogeneity occurrence, which showed that tourniquet application and one surgeon performing TKAs may lead to significant heterogeneity (**Table 2**).

Range of motion (degree)

ROM was mentioned in four RCT articles [13, 15-17]. The results demonstrated that there were significant differences between the celecoxib and placebo groups in TKA patients (MD = 4.70, 95% CI: [3.96, 5.44], P<0.00001, **Figure 5**). There was no heterogeneity between the two groups based on the pooled data (χ^2 = 0.58, df = 3, P = 0.90, I^2 = 0%).

Postoperative nausea and vomiting (PONV)

The morbidity of postoperative complications, such as nausea and vomiting, were presented in three studies [13, 16]. Comparing the celecoxib and placebo groups, a significant difference was confirmed according to the extracted data (RR = 0.68, 95% CI: [0.40, 1.16], P = 0.16, **Figure 6**). We chose a fixed-effects model rather than a random-effects model due to the low statistical heterogeneity (χ^2 = 0.08, df = 1, P = 0.77, I^2 = 0%).

Total blood loss (mL)

Three articles [13, 15, 16] reported the total blood loss between the celecoxib and placebo groups. There was no significant difference based on the pooled data (MD = -3.03, 95% CI: [-27.23, 21.26], P = 0.81, **Figure 7**). A fixed-effects model was applied because of low statistical heterogeneity through the meta-analysis (χ^2 = 2.83, df = 2, P = 0.24, I^2 = 29%).

Opioid consumption (Meq)

The amount of opioid consumption was recorded in five studies [13, 15-18]. The data indicated that a significant difference existed in two groups (MD = -35.64, 95% CI: [-45.61, -25.67], P<0.00001, **Figure 8**). No significant heterogeneity occurred from the forest plot diagram (χ^2 = 3.52, df = 4, P = 0.47, I^2 = 0%), so a fixed-effects model was used.

Other outcomes

Because of insufficient data in some articles, some other confirmed measurement results were not conducted for meta-analysis. KSS was used by Schroer [17] to evaluate the knee status. No significant difference was observed

in DVT and extremities myasthenia between the celecoxib group and placebo group studied by Gong [13]. Meunier [15] noted that the knee injury and osteoarthritis outcome score has no statistical significance.

Discussion

The short-time perioperative application of celecoxib played an important role in the VAS score, ROM, and opioid consumption among patients undergoing primary TKA. In addition, no statistical differences were found in total blood loss and PONV associated with celecoxib use.

Six RCTs met the criteria for meta-analysis. The overall methodological quality of the included studies was relatively high. Four RCTs [13, 15, 17, 19] applied randomized, placebo-controlled, and double-blind strategies, which showed the high quality of the included studies. Huang [16] used an observer-blind study design only. Baseline data were provided in all included studies, yet no intention-to-treat analysis was mentioned. When explaining the results of our study, attention should be paid to methodological weaknesses.

The VAS pain score was a useful indicator to evaluate the pain intensity with high sensitivity [22, 23]. A 10-cm horizontal line is drawn on paper. One side of the horizontal line is zero, stands for painless; on the other side of the paper is ten, which means a sharp pain; middle sections show different degrees of pain. This systematic review showed significant differences of short-term VAS scores between two groups, which mean that celecoxib can effectively alleviate postoperative pain at rest or on ambulation in the short term. Meunier [19] reported that no differences were found in VAS and ROM with a 2-year follow-up. However, significant heterogeneity was shown in VAS pain score on ambulation. Subgroup analysis was performed to investigate the reasons of heterogeneity. The results showed that tourniquet application and one surgeon performing TKA might be the causes of heterogeneity. In addition, some other factors also cannot be ignored, such as patient's subjective cognition and surgery time.

ROM was also an important indicator to reflect the motion of knee joints and evaluate functional rehabilitation [24, 25]. Some scholars believed that ROM as an index of evaluation function and the anesthesia efficacy was significant after TKA [26]. Four studies [13, 15-17] provided the data of ROM. Knee flexion was measured at different time periods; our meta-analysis showed that a significant difference existed between the celecoxib and control groups ($P<0.00001$). Thus, motion of the knee joint could be elevated by short-time celecoxib consumption. Schroer [17] conducted a Kaplan-Meier analysis to research the time to achieve 90 degrees of knee flexion after TKA; eventually the results showed that the celecoxib group reached 90 degrees at 1 month postoperatively, earlier than the control group. Thus, we concluded that perioperative celecoxib consumption had beneficial effects to achieve knee function earlier.

Mean opioid consumption was also a primary outcome, which showed significant difference in our systematic review ($P<0.00001$). Different units of measurement and opioid drugs were used to record opioids consumption. We converted opioid use in all articles to morphine equivalents (Meq). To compare the morphine equivalents of the celecoxib group versus placebo group, five studies were documented to perform meta-analyses. Among elderly patients, they would be easily addicted to opioid medications largely used after TKA [27]; this can cause serious consequences, such as drug dependence, drug tolerance, psychiatric symptoms, urinary retention, and muscle spasm. Therefore, reducing opioid consumption was becoming an increasingly meaningful event. The pooled data showed that celecoxib could decrease the postoperative consumption of opioids. These attractive outcomes mean that less morphine consumption can achieve ideal analgesic effects.

Three studies [13, 16, 18] reported the PONV. PONV was a common manifestation usually caused by different anesthetic techniques [28]. Other reasons [29], such as hypotension, age and gender of patients, premedication, and hydration, were also risk factors of PONV. In our study, there were no significant differences found in PONV ($P = 0.16$). Perioperative celecoxib use could not decrease the incidence of PONV. Some studies [30, 31] also showed that reduced opioid consumption could decrease PONV rates.

Table 3. Results of meta-analysis

Outcome	Studies	Overall effect			Heterogeneity	
		Effect estimate	95% CI	*P* value	I^2 (%)	*P* value
VAS-rest	4	-0.96	-1.19, -0.74	<0.00001	23	0.27
VAS-ambulation	3	-0.88	-1.46, -0.30	0.003	85	0.001
ROM	4	4.70	3.96, 5.44	<0.00001	0	0.9
PONV	3	0.87	0.55, 1.38	0.55	33	0.23
Total blood loss	3	-3.03	-27.32, 21.26	0.81	29	0.24
MOS	5	-35.64	-45.61, 25.67	<0.00001	0	0.57

VAS: Visual Analogue Scale, ROM: Range of Motion, PONV: Postoperative Nausea and Vomiting, MOS: Mean Opioid Consumption.

Blood loss was usually caused by extensive soft tissue injury and massive bone resection, especially among elderly people suffering from TKA. Recently, a study showed that fracture operations and joint arthroplasty require transfusions, accounting for 9.8% of all blood transfusion volume [32]. However, no significant difference was found in total blood loss between two groups according to our meta-analysis (P = 0.81). This indicated that celecoxib would not increase the risk of bleeding compared with the placebo group.

Our systematic review has the following potential limitations: (1) Only six RCTs were selected in our meta-analysis; if more studies were included, statistical efficacy would increase. (2) The follow-up period of patients was too short in some of the trials. Most patients were followed up in the short term (less than 7 days). This may have resulted in underreporting some useful information. (3) There were not sufficient data, such as KSS, DVT, PCS, OKS, and MCS mentioned above. (4) Risk of bias cannot be avoided in this meta-analysis because only English publications were included. Although this study has several limitations, it is the first systematic review to evaluate the effect of perioperative celecoxib use in primary TKA and THA. Available articles were screened strictly; hence, the final adopted articles were of high quality. However, more high-quality literature should be included to elevate statistical efficacy and increase sample size.

Conclusions

This systematic review discusses the efficacy of perioperative celecoxib use (**Table 3**). Celecoxib can decrease the postoperative pain and reduce opioid consumption, as well as elevating knee joint motion. However, celecoxib cannot reduce the incidence of postoperative nausea and vomiting and has no effect on total surgical blood loss, which means celecoxib does not increase the risk of bleeding.

Acknowledgements

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Disclosure of conflict of interest

None.

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