The efficacy of celecoxib for pain management of arthroscopy
A meta-analysis of randomized controlled trials
Ruijie Wan, MD\textsuperscript{a,∗}, Pin Li, MD\textsuperscript{a}, Heng Jiang, MD\textsuperscript{b}

Abstract
Background: The efficacy of celecoxib for pain management of arthroscopy remains controversial. We conduct a systematic review and meta-analysis to assess if celecoxib before the surgery decreases postoperative pain intensity of arthroscopy.

Methods: We search PubMed, Embase, Web of science, EBSCO, and Cochrane library databases for randomized controlled trials (RCTs) assessing the effect of celecoxib versus placebo on pain control of arthroscopy.

Results: Five RCTs are included in the meta-analysis. Celecoxib is administered at 200mg or 400mg dosage before the surgery. Overall, compared with control group for arthroscopy, preemptive celecoxib has remarkably positive impact on pain scores at 2 to 6 hours (standard mean difference (SMD) = −0.66; 95% confidence interval (CI) = −0.95 to −0.36; \( P < 0.0001 \)) and 24 hours after the surgery (SMD = −1.16; 95% CI = −1.83 to −0.50; \( P < 0.0001 \)), analgesic consumption (SMD = −2.73; 95% CI = −5.17 to −0.28; \( P = .03 \)), as well as the decrease in adverse events (risk ratio (RR) = 0.56; 95% CI = 0.39 to 0.79; \( P = .001 \)), but shows no obvious effect on first time for analgesic requirement (SMD = 0.02; 95% CI = −0.22 to 0.26; \( P = .87 \)), nausea, or vomiting (RR = 0.70; 95% CI = 0.42 to 1.17; \( P = .18 \)).

Conclusion: Celecoxib administered at 200mg or 400mg dosage before the surgery decreases postoperative pain intensity of arthroscopy.

Abbreviations: CI = confidence interval, RCTs = randomized controlled trials, SMD = standard mean difference.

Keywords: arthroscopy, celecoxib, meta-analysis, pain management, randomized controlled trials

1. Introduction
Arthroscopy has been widely used for the treatment of knee and hip diseases\textsuperscript{[1–3]} Many patients still encounter moderate to severe pain, although arthroscopic surgery has less morbidity compared with open procedures\textsuperscript{[4–6]} This pain is caused by the insertion of arthroscopic instruments into the joint, soft tissue dissection, and distention caused by the irrigation of joint\textsuperscript{[7,8]} Inadequate management of perioperative pain can lead to prolonged hospital stays, delayed recovery, poor outcomes, and greater consumption of health care resources\textsuperscript{[9–11]}

Celecoxib is known as the selective cyclooxygenase (COX)-2 inhibitor, and has the properties of rapid absorption, high oral bioavailability, and preferential distribution into inflamed tissue\textsuperscript{[12,13]} Celecoxib may have the ability to prevent heterotopic bone formation for arthroscopy\textsuperscript{[14]} In one recent study, celecoxib administered 1 hour before arthroscopic surgery of hip benefits to pain control at 12 and 24hours postoperatively and leads to the increase in physical composite score\textsuperscript{[15]}

However, the efficacy of celecoxib versus placebo for pain management of arthroscopy has not been well established. Recently, several studies on the topic have been published, and the results have been conflicting\textsuperscript{[15–18]} With accumulating evidence, we therefore perform a systematic review and meta-analysis of randomized controlled trials (RCTs) to assess if celecoxib before the surgery decreases postoperative pain intensity of arthroscopy.

2. Materials and methods
Ethical approval and patient consent are not required because this is a systematic review and meta-analysis of previously published studies. The systematic review and meta-analysis are conducted and reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)\textsuperscript{[19]}

2.1. Search strategy and study selection
Two investigators have independently searched the following databases (inception to November 2018): PubMed, Embase, Web of science, EBSCO, and Cochrane library databases. The
electronic search strategy is conducted using the following keywords: celecoxib and arthroscopy. We also checked the reference lists of the screened full-text studies to identify other potentially eligible trials.

The inclusive selection criteria are as follows:

(1) population: patients undergo arthroscopy;
(2) intervention treatments are celecoxib versus placebo;
(3) study design is RCT.

2.2. Data extraction and outcome measures
We have extracted the following information: author, number of patients, age, female, body mass index, duration of surgery, detail methods in each group, and so on. Data have been extracted independently by two investigators, and discrepancies are resolved by consensus. We also contact the corresponding author to obtain the data when necessary.

The primary outcomes are pain scores at 2–6 hours and 24 hours after the surgery. Visual analogue scale (VAS) is used to evaluate the pain intensity (VAS 0, no pain and 10, the worst unbearable pain). Secondary outcomes include analgesic consumption, first time for analgesic requirement, adverse events, nausea, and vomiting.

2.3. Quality assessment in individual studies
Methodological quality of the included studies is independently evaluated using the modified Jadad scale. There are 3 items for Jadad scale: randomization (0–2 points), blinding (0–2 points), and dropouts and withdrawals (0–1 points). The score of Jadad scale varies from 0 to 5 points. An article with Jadad score ≤ 2 is considered to be of low quality. If the Jadad score ≥ 3, the study is thought to be of high quality.

2.4. Statistical analysis
We estimate the standard mean difference (SMD) with 95% confidence interval (CI) for continuous outcomes (pain scores at 2–6 hours and 24 hours after the surgery, analgesic consumption, and first time for analgesic requirement) and risk ratios (RRs) with 95% CIs for dichotomous outcomes (adverse events, nausea, and vomiting). The random-effects model is used regardless of heterogeneity. Heterogeneity is reported using the $I^2$ statistic, and $I^2 > 50\%$ indicates significant heterogeneity. Whenever significant heterogeneity is present, we search for potential sources of heterogeneity via omitting one study in turn for the meta-analysis or performing subgroup analysis. All statistical analyses are performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

3. Results
3.1. Literature search, study characteristics, and quality assessment
A detailed flowchart of the search and selection results is shown in Fig. 1. About 443 potentially relevant articles are identified initially. Finally, five RCTs are included in the meta-analysis.

The baseline characteristics of five eligible RCTs in the meta-analysis are summarized in Table 1. The five studies are published between 2006 and 2017, and the total sample size is 548. There are knee and hip arthroscopies in the included RCTs. The study conducted by Mardani-Kivi et al for knee arthroscopic surgery of meniscectomy, while Mardani-Kivi 2013 (2) represented the same study for knee arthroscopic surgery of anterior cruciate ligament reconstruction. Celecoxib is administered at 200 mg or 400 mg dosage before the surgery.

Among the five studies included here, two studies report pain scores at 2 to 6 hours after the surgery, one study reports pain scores at 24 hours after the surgery, and two studies report analgesic consumption. Two studies report first time for analgesic requirement, two studies report adverse events, and two studies report nausea and vomiting.

Jadad scores of the five included studies vary from 3 to 5, and all five studies are considered to be high-quality ones according to quality assessment.

3.2. Primary outcomes: pain scores at 2–6 hours and 24 hours after the surgery
These outcome data are analyzed with the random-effects model, and compared to control group for arthroscopy, preemptive celecoxib results in significantly lower pain scores at 2 to 6 hours after the surgery (SMD = –0.66; 95% CI = –0.95 to –0.36; $P < .0001$) with low heterogeneity among the studies ($I^2 = 13\%$, heterogeneity $P = .32$) (Fig. 2A), and pain scores at 24 hours after the surgery (SMD = –1.26; 95% CI = –1.83 to –0.70; $P < .0001$) with significant heterogeneity among the studies ($I^2 = 50\%$, heterogeneity $P = .16$) (Fig. 2B).

3.3. Sensitivity analysis
Significant heterogeneity is observed among the included studies for pain scores at 24 hours after the surgery, but there is just one RCT reporting knee arthroscopic surgery of meniscectomy and anterior cruciate ligament reconstruction. It is not available to perform sensitivity analysis via omitting one study in turn.

3.4. Secondary outcomes
In comparison with control group for arthroscopy, preemptive celecoxib is associated with substantially reduced analgesic consumption (SMD = –2.73; 95% CI = –5.17 to –0.28; $P = .03$; Fig. 2C), but exhibits no obvious effect on first time for analgesic requirement (SMD = 0.02; 95% CI = –0.22 to 0.26; $P = .87$; Fig. 2D). In addition, preemptive celecoxib leads to the decrease in adverse events (RR = 0.56; 95% CI = 0.39 to 0.79; $P = .001$; Fig. 2E), but shows no significant impact on nausea or vomiting (RR = 0.70; 95% CI = 0.42 to 1.17; $P = .18$; Fig. 2F).

4. Discussion
Celecoxib is a novel selective COX-2 inhibitor, and has the property of preferential distribution into inflamed tissue. Celecoxib is reported to be superior to lumiracoxib, and has become the first-choice analgesic agent for osteoarthritis pain. Celecoxib has proved to be beneficial for pain control in various orthopedic surgeries. Patients receiving 400 mg of celecoxib 1 hour before knee arthroscopy have reduced consumption of opioid medication and incidence of opioid-related adverse events.
in the early postoperative period. In another study, the decrease in pain intensity and opioid consumptions, as well as the increase in knee range of motion are observed after celecoxib use for knee arthroplasty.

In addition, celecoxib before the surgery is proved to be more effective for pain control than that given postoperatively. Our meta-analysis suggests that compared to control group for arthroscopy, preemptive celecoxib shows favorable influence on pain control at 2–6 hours and 24 hours after the surgery, as well as postoperative analgesic consumption, but reveals no obvious impact on first time for analgesic requirement. However, there is significant heterogeneity when performing sensitivity analysis and this heterogeneity may be caused by different procedures of arthroscopy, various doses of celecoxib, and the time of drug use.

Traditional pain management after orthopedic surgery mainly requires the use of narcotic medications, but narcotic medications may have severe side effects on the gastrointestinal, respiratory, integumentary, genitourinary, and neurologic systems. In order to reduce these side effects, multimodal pain management has been extensively developed for pain control. Multimodal pain management aims to target multiple pathways in the pain signaling cascade to minimize pain intensity and side effects. Celecoxib has emerged as an increasing important drug for multimodal pain management. The results of our

Figure 1. Flow diagram of study searching and selection process.
| No. | Author               | Number | Age (yrs) | Female (n) | Body mass index (kg/m²) | Duration of surgery (min) | Methods                                                                 | Number | Age (yrs) | Female (n) | Body mass index (kg/m²) | Duration of surgery (min) | Methods       | Jada scores |
|-----|----------------------|--------|-----------|------------|------------------------|--------------------------|--------------------------|--------|-----------|------------|------------------------|--------------------------|---------------|-------------|
| 1   | Kahlenberg 2017      | 50     | 34.2 ± 11.9 | 26         | –                      | 95.4 ± 20.2              | 400 mg celecoxib administered 1h before hip arthroscopy                  | 48     | 35.8 ± 11.6 | 29         | –                      | 95.8 ± 17.3              | Matched placebo | 4           |
| 2   | Zhang 2014           | 27     | 41.0 ± 4.9  | 13         | 33 ± 5.1               | 67 ± 7                   | 200 mg celecoxib administered 1h preoperatively for arthroscopic hip surgery | 26     | 43.5 ± 5.1  | 15         | 35 ± 4.9               | 90 ± 3                   | Matched placebo | 5           |
| 3   | Mardani-Kivi 2013 (1)| 31     | 32.7 ± 8    | 22         | 24 ± 2.7               | 30.3 ± 7                 | 400 mg celecoxib administered 2h before knee arthroscopic surgery of meniscectomy | 32     | 32.2 ± 9.8  | 20         | 23 ± 2.6               | 31.7 ± 4                 | Matched placebo | 4           |
|     | Mardani-Kivi 2013 (2)| 34     | 25.8 ± 7.7  | 28         | 24 ± 2.6               | 40 ± 7                   | 400 mg celecoxib administered 2h before knee arthroscopic surgery of anterior cruciate ligament reconstruction | 33     | 26.7 ± 4.9  | 25         | 23.6 ± 3.5             | 36.7 ± 7                 | Matched placebo | 4           |
| 4   | Boonfon 2010         | 35     | 30         | 4          | –                      | 60.73 ± 14.20            | 400 mg celecoxib administered 1h before arthroscopic anterior cruciate ligament reconstruction | 32     | 30         | 4          | –                      | 60.45 ± 20.30           | Matched placebo | 3           |
| 5   | Broman 2006          | 99     | 45.5 ± 11.1 | 46         | –                      | –                        | 400 mg celecoxib administered 1h before arthroscopic knee meniscectomy    | 101    | 45.0 ± 10.9 | 39         | –                      | –                       | Matched placebo | 4           |
meta-analysis show significant decrease in adverse events after using preemptive celecoxib for arthroscopy.

This meta-analysis has several potential limitations. First, our analysis is based on five RCTs, and three of them have a relatively small sample size (n < 100). Overestimation of the treatment effect is more likely in smaller trials compared with larger samples. Second, there is significant heterogeneity which may result from different procedures of arthroscopy, various doses of celecoxib, and the time of drug use. Finally, it is feasible to perform the meta-analysis of some important outcomes such as pain scores in longer time of follow-up and discharge time based on current RCTs.
5. Conclusions
In conclusion, celecoxib administered at 200 mg or 400 mg dosage before the surgery decreases postoperative pain intensity of arthroscopy.

Acknowledgments
None.

Author contributions
Conceptualization: Ruijie Wan.
Data curation: Ruijie Wan.
Funding acquisition: Pin Li.
Methodology: Ruijie Wan, Pin Li.
Project administration: Pin Li.
Supervision: Heng Jiang.
Writing – original draft: Heng Jiang.
Writing – review & editing: Heng Jiang.

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