Systematic Review and Meta-Analysis

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# The analgesic evaluation of gabapentin for arthroscopy

## A meta-analysis of randomized controlled trials

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**Abstract**

**Introduction:** The efficacy of gabapentin for pain management of arthroscopy remains controversial. We conduct a systematic review and meta-analysis to explore the influence of gabapentin versus placebo on the postoperative pain intensity of arthroscopy.

**Methods:** We search PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases through April 2020 for randomized controlled trials assessing the effect of gabapentin versus placebo on pain control of arthroscopy. This meta-analysis is performed using the random-effect model.

**Results:** Five randomized controlled trials are included in the meta-analysis. Overall, compared with control group for arthroscopy, gabapentin remarkably decreases pain scores at 24 hour (standard mean difference [SMD]=-0.68; 95% confidence interval [CI]=-1.15 to -0.02; $P=.21$), analgesic consumption (SMD = -18.24; 95% CI=-24.61 to -11.88; $P<.00001$), nausea and vomiting (OR=0.42; 95% CI=0.21 to 0.84; $P=.01$), but has no obvious influence on pain scores at 6 h (SMD=−1.30; 95% CI=−2.92 to 0.31; $P=.11$) or dizziness (OR=1.12; 95% CI=0.56 to 2.24; $P=.75$).

**Conclusions:** Gabapentin is effective for pain control after arthroscopy.

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

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

## 1. Introduction

Arthroscopy has been extensively developed for the diseases of shoulder, knee, and hip.[1–4] Moderate to severe pain commonly occurs after arthroscopic surgery, and results from insertion of arthroscopic instruments into the joint, bone removal, soft tissue dissection, and distention.[5–9] Multimodal analgesia is developed to target the routes of nerves and various neurotransmitters to inhibit hyperalgesia and nociception.[10] It may also improve inflammatory and neurogenic conditions.[11]

Gabapentin was used as an anti-epileptic drug and was subsequently applied for acute and chronic pain associated with different diseases such as post-herpetic neuralgia, diabetic neuropathy, trigeminal neuralgia and various headaches.[12] It acts through binding to the alpha 2-delta-subunit of voltage-gated calcium channels and inhibiting the release of nociceptive neurotransmitters including glutamates, P-substance and norepinephrine from presynaptic afferent neurons.[13] The anti-hyperalgesic feature of gabapentin may focus on the reduction of pathologic postoperative pain.[14] In a systematic review, gabapentin was reported to reduce pain significantly and decrease the need to opioids.[15] In contrast, a systematic narrative review of 22 randomized clinical trial studies indicated that gabapentin as a single dose preemptive analgesia did not reduce pain and opioid consumption.[16,17]

The application of gabapentin for the pain management of arthroscopy is not fully explored, and several studies reported the conflicting results.[18–20] With accumulating evidence, we therefore perform a systematic review and meta-analysis of randomized controlled trials (RCTs) to explore the efficacy and safety of gabapentin in patients with 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).[21,22]

### 2.1. Search strategy and study selection

Two investigators have independently searched the following databases (inception to April 2020): PubMed, EMbase, Web of

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science, EBSCO, and Cochrane library databases. The electronic search strategy is conducted using the following keywords: gabapentin, and arthroscopy. We also check the reference lists of the screened full-text studies to identify other potentially eligible trials.

The inclusive selection criteria are as follows:

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

### 2.2. Data extraction and outcome measures

We have extracted the following information: author, number of patients, age, female, body weight, duration of surgery and 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 6 hour and 24 hour. Secondary outcomes include analgesic consumption, dizziness, nausea, and vomiting.

### 2.3. Quality assessment in individual studies

Methodological quality of the included studies is independently evaluated using the modified Jadad scale.[23] There are 3 items for Jadad scale: randomization (0-2 points), blinding (0-2 points), dropouts and withdrawals (0-1 points). The score of Jadad Scale varies from 0 to 5 points. An article with Jadad score$\leq$2 is considered to be of low quality. If the Jadad score $\geq$3, the study is thought to be of high quality.[24]

### 2.4. Statistical analysis

We estimate the standard mean difference (SMD) with 95% confidence interval (CI) for continuous outcomes (pain scores at 6 hour and 24 hour, analgesic consumption) and odd ratio (OR) with 95% CIs for dichotomous outcomes (dizziness, 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.[22,25] 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).

## 3. Results

### 3.1. Literature search, study characteristics and quality assessment

A detailed flowchart of the search and selection results is shown in Figure 1. 261 potentially relevant articles are identified initially. Finally, five RCTs that meet our inclusion criteria are included in the meta-analysis.[18–20,26,27]

The baseline characteristics of the five eligible RCTs in the meta-analysis are summarized in Table 1. The three studies are published between 2006 and 2016, and total sample size is 346. The doses of gabapentin include 300 mg,[26] 600 mg,[18,19] or 800 mg[27] before the surgery. Another included RCT involve 300 mg of gabapentin before surgery, then twice a day for 2 days.[20]

Among the five studies included here, two studies report pain scores at 6 h,[18,19] three studies report pain scores at 24 hour,[18–20] two studies report analgesic consumption,[18,19] four studies report dizziness,[18–20,26] as well as four studies report nausea and vomiting.[18,19,26,27] 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 6 hour and 24 hour

These outcome data are analyzed with the random-effects model, and compared to control group for arthroscopy, gabapentin shows no obvious impact on pain scores at 6 hour (SMD = −1.30; 95% CI = −2.92 to 0.31; $P = .11$) with significant heterogeneity among the studies ($I^2 = 93\%$, heterogeneity $P = .0002$) (Fig. 2), but is associated with significantly reduced pain scores at 24 hour (SMD = −0.68; 95% CI = −1.15 to -0.02; $P = .21$) with no heterogeneity among the studies ($I^2 = 0\%$, heterogeneity $P = .53$) (Fig. 3).

### 3.3. Sensitivity analysis

Significant heterogeneity is observed among the included studies for pain scores at 6 hour. There are just two included RCTs, so we do not perform sensitivity analysis via omitting one study in turn to detect the heterogeneity.

### 3.4. Secondary outcomes

In comparison with control group for arthroscopy, gabapentin can substantially reduce analgesic consumption (SMD = −18.24; 95% CI = −24.61 to -11.88; $P < .00001$; Fig. 4), but exhibits no obvious impact on dizziness (OR = 1.12; 95% CI = 0.56 to 2.24; P = 0.75; Fig. 5). In addition, the incidence of nausea and vomiting is found to be lower in gabapentin group than that in control group (OR = 0.42; 95% CI = 0.21 to 0.84; $P = .01$; Fig. 6).

## 4. Discussion

Many methods have been developed to reduce postoperative pain after arthroscopic surgery, and include infiltration of local anesthetic, nerve block and interscalene block.[28–30] However, they are limited by procedural difficulties and complications inherent in their invasive nature.[31] Non-steroidal anti-inflammatory drugs and opioid drugs are commonly used for the postoperative pain control, but may lead to nausea, vomiting and gastrointestinal bleeding. Thus, multimodal analgesia is developed to reduce these opioid-related adverse effect.[32]

Gabapentinoids were found to interact with other analgesics additively or synergistically to decrease inflammatory hyperalgesia, and decrease opioid consumption.[33,34] Gabapentin on postoperative pain was studied in different surgical interventions, and showed obvious decrease in pain intensity and opioid consumption in hysterectomy and spinal surgery.[35] In orthopedic and musculoskeletal surgeries, the pain intensity and opioid consumption at 24 hour follow-up visit was significantly reduced among patients taking gabapentin.[27,36–38] Arthroscopic surgery, as a minimally-invasive procedure, has been increasing, but only limited numbers of studies examining the effectiveness of gabapentin in arthroscopic surgeries.[20,26,27] Our meta-analysis includes five RCTs involving 346 patients, and the results suggest that gabapentin is associated with substantially reduced pain

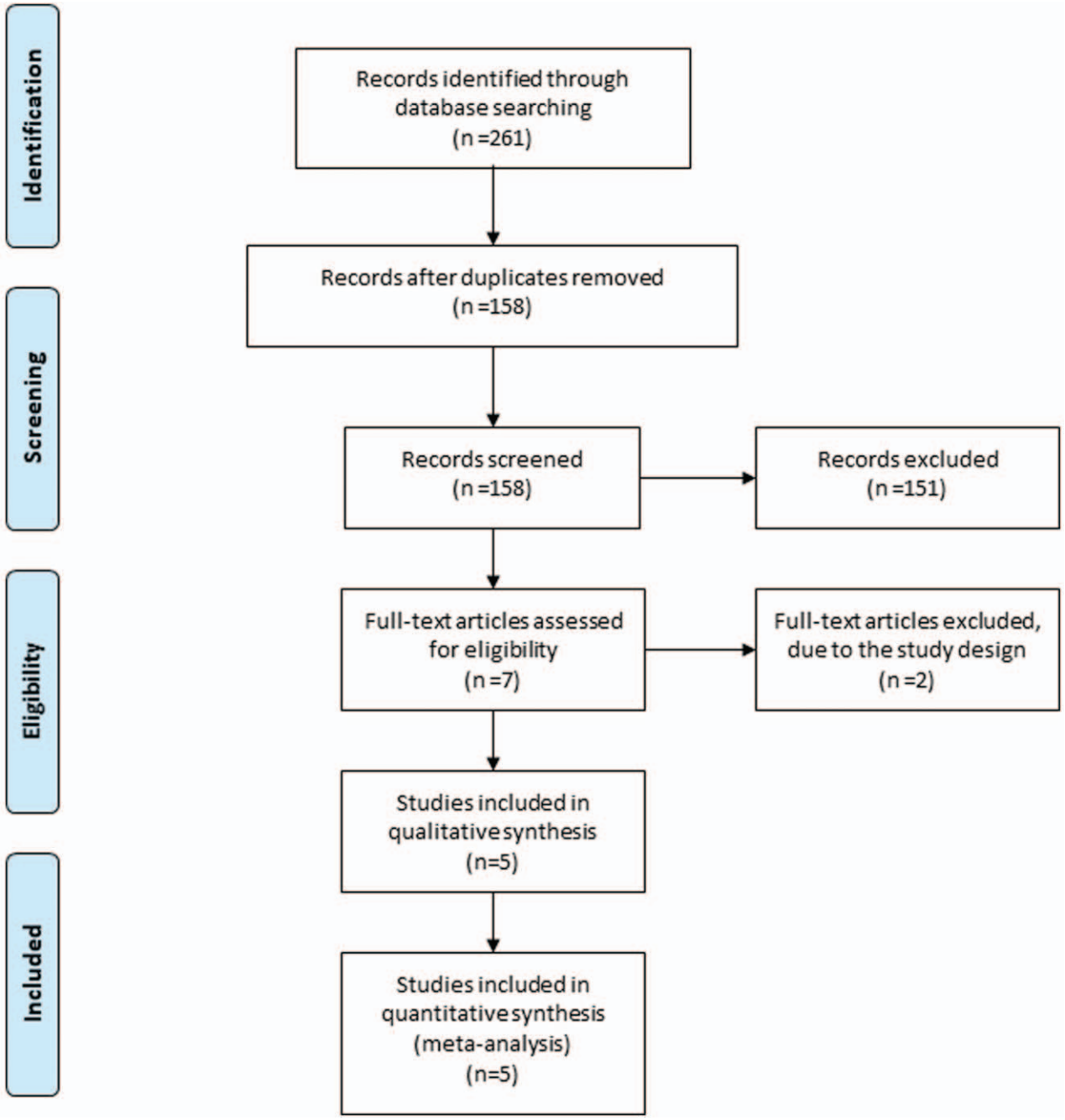


**Figure 1.** Flow diagram of study searching and selection process.

scores at 24 hour and analgesic consumption for arthroscopy, but has no remarkable influence on pain scores at 6 hour.

The efficacy in administration of gabapentin as a preemptive analgesic reported may be caused by the differences in gabapentin dosages, the time of the administration of gabapentin, being a single dose or multiple doses, and anesthesia method. The included RCTs reported different doses of gabapentin including 300 mg,[26] 600 mg,[18,19] or 800 mg[27] before the surgery, as well as 300 mg of gabapentin before surgery, then twice a day for 2 days.[20] A meta-analysis of 1151 patients (614 patients taking gabapentin in 16 RCTs) included three categories according to the gabapentin dosages: A. a single dose of 1200 mg; B. a single dose less than 1200 mg; C. multiple dose of less than 1200 mg. The results revealed that patients with a single dose of gabapentin experienced significantly less pain than the placebo group, and gabapentin group results in significantly more sedation, but less vomiting and pruritus.[39] 600 mg dosage of gabapentin was more effective than 300 mg dosage and has the same effectiveness as higher dosages (900 and 1200 mg) in reducing pain intensity and total opioid consumption.[40] Repeated multi-doses of gabapentin increase the side effects especially sedation.[18] These recommend a single dose of 600 mg gabapentin for the pain control after arthroscopy, but more studies should be conducted to confirm this issue.

**Table 1**

**Characteristics of included studies.**

| | | Gabapentin group | | | | | | Control group | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NO. | Author | Number | Age (yr) | Female (n) | Weight (kg) | Duration of surgery (min) | Methods | Number | Age (yr) | Female (n) | Weight (kg) | Duration of surgery (min) | Methods | Jada scores |
| 1 | Mardani-Kivi 2016 | 38 | 30.2±5 | 11 | 68.2±1.8 | 46.9±10.7 | gabapentin 600 mg, 2 h before surgery | 38 | 28.3±4.4 | 8 | 67.4±11.3 | 43.9±9.5 | placebo | 4 |
| 2 | Kivi 2013 | 57 | 32.2±9.3 | 8 | 74.9±9.4 | 40±10 | gabapentin 600 mg | 57 | 30.5±10.2 | 6 | 73.6±8.5 | 36±7 | placebo | 4 |
| 3 | Spence 2011 | 26 | 31.8±10.48 | 4 | – | – | 300 mg of gabapentin 1 h before surgery, then twice a day for 2 d | 31 | 31.51±8.9 | 5 | – | – | placebo | 3 |
| 4 | Bang 2010 | 23 | 56.3±8.5 | 14 | 63.9±11.8 | 104.7±35.8 | gabapentin 300 mg, 2 h before surgery | 23 | 59.5±6.2 | 15 | 64.2±8.4 | 98.7±23.7 | placebo | 4 |
| 5 | Adam 2006 | 27 | 43±18 | 9 | 70±12 | 57±31 | gabapentin 800 mg, 2 h before surgery | 26 | 47±15 | 8 | 74±13 | 57±27 | placebo | 4 |

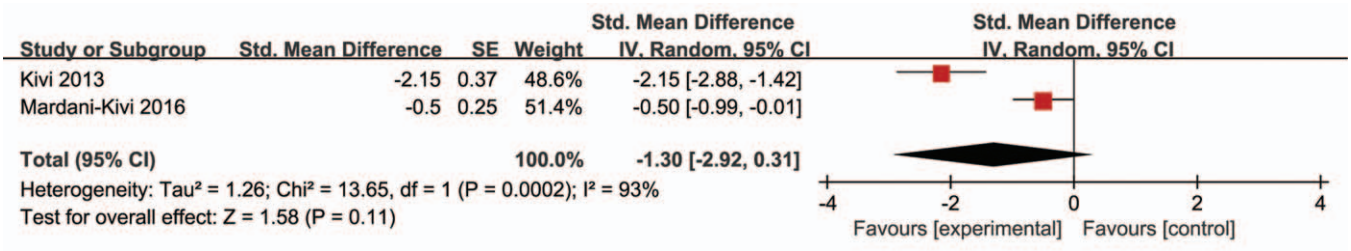


**Figure 2.** Forest plot for the meta-analysis of pain scores at 6 h.

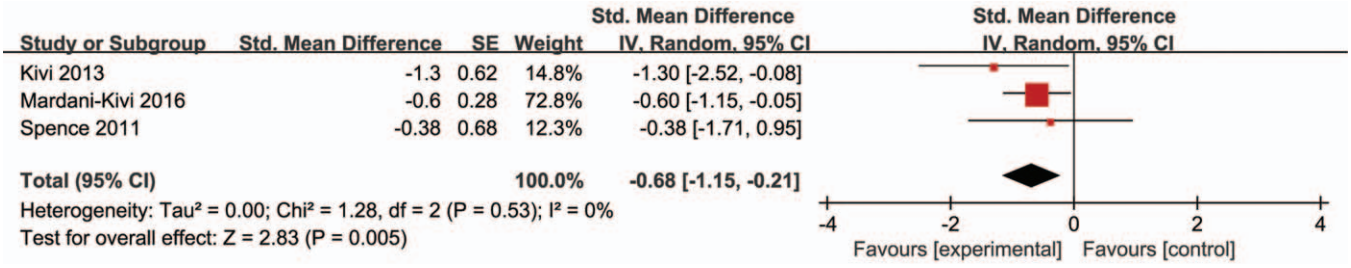


**Figure 3.** Forest plot for the meta-analysis of pain scores at 24 h.

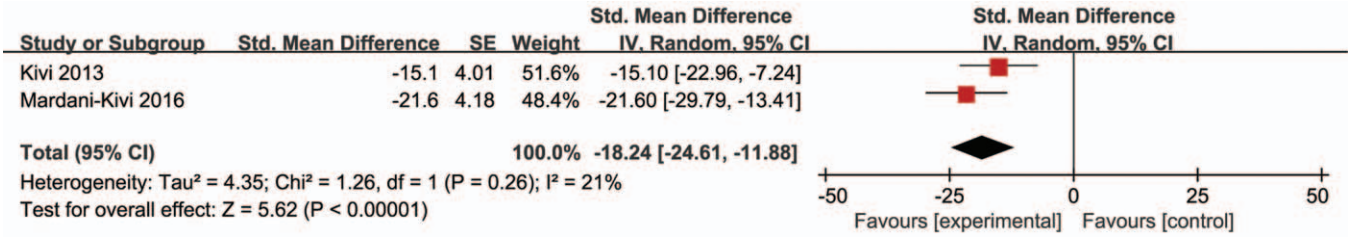


**Figure 4.** Forest plot for the meta-analysis of analgesic consumption.

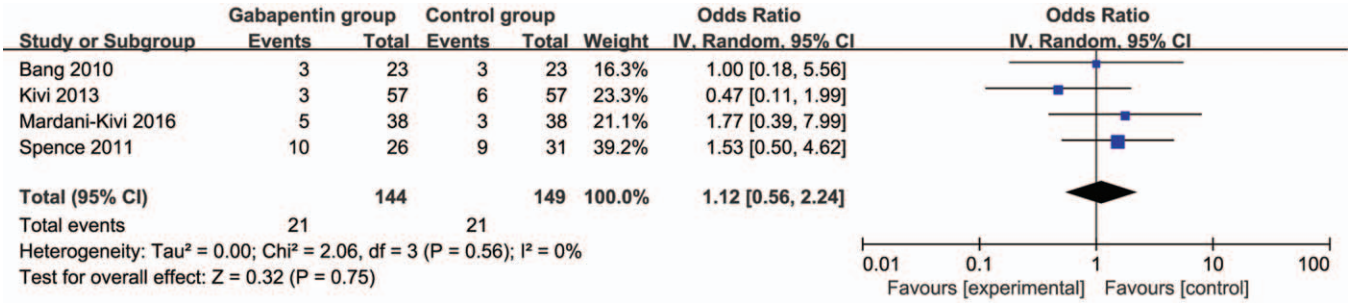


**Figure 5.** Forest plot for the meta-analysis of dizziness.

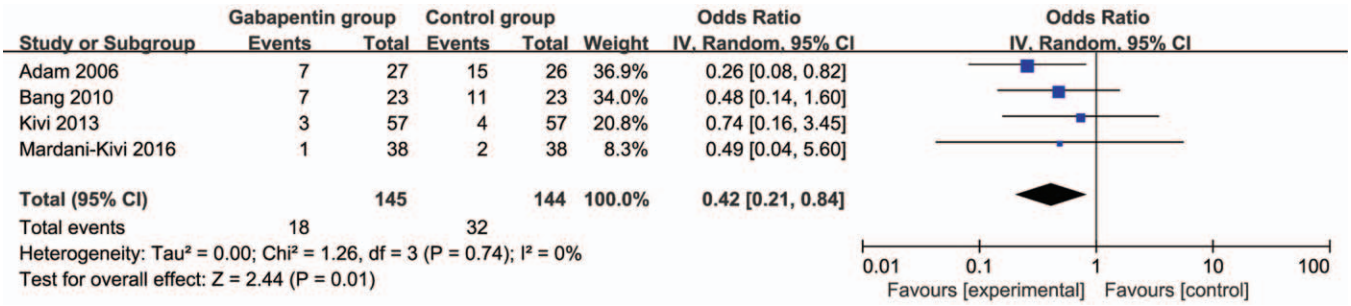


**Figure 6.** Forest plot for the meta-analysis of nausea and vomiting.

Gabapentin 2 hours preoperatively is recommended to administer because it can achieve the maximum plasma concentration 2-3 h after taking the drug. Since gabapentin has no hepatic metabolism and is excreted without change through the kidneys, gabapentin is well tolerant.[18,41] In this meta-analysis, gabapentin shows no increase in dizziness, but is associated with the decrease in nausea and vomiting, which may be derived from the reduction of analgesic consumption after the surgery. This meta-analysis has several potential limitations. Firstly, our analysis is based on five RCTs, and all 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. Next, there is significant heterogeneity for pain scores at 6 hour, which may be caused by different methods of gabapentin and operation procedures. Finally, it is not feasible to perform the meta-analysis of some important index such as pain scores at longer follow up time and perform the subgroup analysis based on dosages.

## 5. Conclusions

Gabapentin is effective and safe to relieve the pain after arthroscopy.

## Author contributions

**Conceptualization:** Feiri Huang.
**Data curation:** Feiri Huang, Xiaosheng Gao.
**Formal analysis:** Feiri Huang, Xiaosheng Gao.
**Methodology:** Zhifang Yang.
**Software:** Zhongliang Su.
**Writing – original draft:** Xiaosheng Gao.
**Writing – review & editing:** Xiaosheng Gao.

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