The efficacy of intra-articular fentanyl supplementation for knee arthroscopy: A meta-analysis of randomized controlled studies

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Abstract
Introduction: The efficacy of intra-articular fentanyl supplementation for pain control after knee arthroscopy remains controversial. We conduct a systematic review and meta-analysis to explore the influence of intra-articular fentanyl supplementation for pain intensity after arthroscopic knee surgery. Methods: We searched PubMed, EMbase, Web of Science, EBSCO, and Cochrane Library databases through May 2019 for randomized controlled trials (RCTs) assessing the efficacy and safety of intra-articular fentanyl supplementation for arthroscopic knee surgery. This meta-analysis is performed using the random-effects model. Results: Four RCTs are included in the meta-analysis. Overall, compared with control group after knee arthroscopy, intra-articular fentanyl supplementation is associated with reduced pain scores at 1 h (standard mean difference (Std MD) = −3.50; 95% confidence interval (CI) = −5.68 to −1.32; p = 0.002), 2 h (Std MD = −4.73; 95% CI = −8.75 to −0.71; p = 0.02), and 8 h (Std MD = −5.02; 95% CI = −9.73 to −0.30; p = 0.04) but shows no substantial impact on pain scores at 4 h (Std MD = −3.94; 95% CI = −7.93 to 0.05; p = 0.05) or the supplementary analgesia (risk ratio = 0.56; 95% CI = 0.09–3.59; p = 0.54). Conclusions: Intra-articular fentanyl supplementation does benefit in pain control after knee arthroscopy.

Keywords
intra-articular fentanyl, knee arthroscopy, pain control, randomized controlled trials

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Introduction
Arthroscopic knee surgeries are widely used day case surgeries, but patients commonly suffer pain after the surgery. Postoperative pain has become one important obstacle to delay hospital discharge and prevent early rehabilitation. Systemic opioid and nonopioid analgesics are commonly applied to alleviate pain by means of different approaches, including central and peripheral nerve blockades and intra-articular drug administration. Intra-articular injection of local anesthetics, such as bupivacaine, is reported to provide efficient analgesia and reduces the number of systemic adverse events. However, intra-articular administration of local anesthetics can provide adequate but short-term analgesia, and thus various adjuvant agents, such as opioids, are added to local anesthetics. Fentanyl has the advantages of high lipophilic property and no
hyperalgesia because of no release of local histamine. Good efficacy and a low incidence of side effects are observed for the control of postoperative pain and acute pain syndromes by fentanyl supplementation.\textsuperscript{13,14} Fifty micrograms of intra-articular fentanyl is revealed to provide better pain relief than 3 mg of intra-articular morphine.\textsuperscript{15}

Current evidence is insufficient for routine clinical use of intra-articular fentanyl supplementation for knee arthroscopy. Recently, several studies have investigated the efficacy and safety of intra-articular fentanyl supplementation for arthroscopic knee surgery, but the results are conflicting.\textsuperscript{15–17} This systematic review and meta-analysis of randomized controlled trials (RCTs) aim to assess the efficacy and safety of intra-articular fentanyl supplementation in patients with arthroscopic knee surgery.

**Materials and methods**

This systematic review and meta-analysis are performed based on the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement and Cochrane Handbook for Systematic Reviews of Interventions.\textsuperscript{18,19} No ethical approval and patient consent are required because all analyses are based on previously published studies.

**Literature search and selection criteria**

We systematically searched several databases, including PubMed, EMBase, Web of Science, EBSCO, and the Cochrane Library from inception to May 2019 with the following keywords: fentanyl and arthroscopic knee surgery or knee arthroscopy. The reference lists of retrieved studies and relevant reviews are also hand-searched and the
The process above is performed repeatedly to include additional eligible studies.

The inclusion criteria are presented as follows: (1) study design is RCT, (2) patients undergo knee arthroscopy, and (3) intervention treatments are intra-articular fentanyl supplementation versus nothing.

**Data extraction and outcome measures**

Some baseline information is extracted from the original studies, and they include first author, number of patients, age, female, height, weight, and detail methods in two groups. Data are extracted independently by two investigators, and discrepancies are resolved by consensus. We have contacted the corresponding author to obtain the data when necessary.

The primary outcome is pain scores at 1 h. Secondary outcomes include pain scores at 2, 4, and 8 h supplementary analgesia.

**Quality assessment in individual studies**

The methodological quality of each RCT is assessed by the Jadad scale, which consists of three evaluation elements: randomization (0–2 points), blinding (0–2 points), and dropouts and withdrawals (0–1 points). One point would be allocated to each element if they have been conducted and mentioned appropriately in the original article. The score of Jadad scale varies from 0 to 5 points. An article with Jadad score ≤ 2 is considered to be of low quality. The study is thought to be of high quality if Jadad score ≥ 3.

**Statistical analysis**

We assess standard mean differences (Std MDs) with 95% confidence intervals (CIs) for continuous outcomes (pain scores at 1, 2, 4, and 8 h) risk ratios (RRs) with 95% CIs for dichotomous outcomes (supplementary analgesia). Heterogeneity is evaluated using the $I^2$ statistic, and $I^2 > 50\%$ indicates significant heterogeneity. The random-effects model is used for all meta-analysis. We search for potential sources of heterogeneity for significant heterogeneity. Sensitivity analysis is performed to detect the influence of a single study on the overall estimate via omitting one study in turn or performing the subgroup analysis. Owing to the limited number (<10) of included studies, publication bias is not assessed. Results are considered as statistically significant for $p$ value < 0.05. All statistical analyses are performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

**Results**

**Literature search, study characteristics, and quality assessment**

Figure 1 shows the detail flowchart of the search and selection results. Four hundred fifty-seven potentially relevant
articles are identified initially. Finally, four RCTs are included in the meta-analysis. 15–17,23

The baseline characteristics of the four included RCTs are presented in Table 1. These studies are published between 1999 and 2015, and the total sample size is 154. Among the included RCTs, intra-articular fentanyl supplementation serves as the adjunctive therapy to levobupivacaine16 and bupivacaine. 17,23 Three studies report pain scores at 1, 2, 4, and 8 h, 15–17 and two studies report supplementary analgesia. 16,17 Jadad scores of the four included studies vary from 3 to 5, and all four studies have high quality based on the quality assessment.

Primary outcomes: pain scores at 1 h

The random-effects model is used for the analysis of the primary outcome. The results find that compared to control group for knee arthroscopy, intra-articular fentanyl supplementation is associated with decreased pain scores at 1 h (Std MD = -3.50; 95% CI = -5.68 to -1.32; p = 0.002), with significant heterogeneity among the studies (I^2 = 93%, heterogeneity p < 0.00001, Figure 2).

Sensitivity analysis

There is significant heterogeneity for pain scores at 1 h. As shown in Figure 2, the study24 shows results that are completely out of range of the others and probably contributes to the heterogeneity. After excluding this study, the results suggest that intra-articular fentanyl supplementation can substantially reduce the pain scores at 1 h after knee arthroscopy (Std MD = -1.90; 95% CI = -2.44 to -1.36; p < 0.00001). No evidence of heterogeneity is observed among the remaining studies (I^2 = 0%).

Secondary outcomes

In comparison with control intervention for knee arthroscopy, intra-articular fentanyl supplementation results in the decrease in pain scores at 2 h (Std MD = -4.73; 95% CI = -8.75 to -0.71; p = 0.02; Figure 3) but demonstrates no obvious impact on pain scores at 4 h (Std MD = -3.94; 95% CI = -7.93 to 0.05; p = 0.05; Figure 4). Intra-articular fentanyl supplementation can also reduce the pain scores at 8 h (Std MD = -5.02; 95% CI = -9.73 to -0.30; p = 0.04; Figure 5) after knee arthroscopy but demonstrates no obvious impact on
supplementary analgesia (RR = 0.56; 95% CI = 0.09–3.59; p = 0.54; Figure 6).

Discussion
Success of arthroscopic knee surgery relies on efficient postoperative pain control and early mobilization. Many analgesia methods are developed for arthroscopy, and they mainly include systemically administered analgesic agents, neuraxial blockades, local anesthetic infiltration, and intra-articular injections. Intra-articular and epidural injections of morphine and bupivacaine are compared in arthroscopies, and intra-articular injections lead to less postoperative pain scores than epidural injections. In addition, intra-articular injection of morphine provides better postoperative pain control compared to intramuscular injection. These indicate that the intra-articular injection of local anesthetics has emerged as an increasing significant method for pain relief after knee arthroscopy.

Intra-articular administration of local anesthetics can afford adequate analgesia, but this analgesia is short-term about 4 h. Various adjuvant agents are added for the intra-articular injection of local anesthetics to prolong the analgesia duration. Combining 50 μg of fentanyl with bupivacaine can prolong the period of analgesic effect to 9 h. Another study comparing the 3 mg of morphine and 50 μg of fentanyl administered intra-articularly with a control group for knee arthroscopy reveals that intra-articular 50 μg fentanyl provides the best promotion to pain relief.

Our meta-analysis suggests that intra-articular fentanyl supplementation can substantially decrease the pain scores at 1, 2, and 8 h after knee arthroscopy but has no significant impact on pain scores at 4 h and the number of patients needing supplementary analgesia. Furthermore, one included RCTs, regarding the addition of fentanyl to levobupivacaine for arthroscopic knee surgery, confirms the better efficacy of intra-articular fentanyl–levobupivacaine for controlling postoperative pain up to 24 h compared to intra-articular levobupivacaine. Twenty patients receiving intra-articular fentanyl–levobupivacaine require 23 times of supplementary analgesia, which is contrast to 43 times in 20 patients receiving intra-articular levobupivacaine. The incidence of adverse event is reported to be similar between intra-articular fentanyl supplementation and control group for knee arthroscopy.

Several limitations exist in this meta-analysis. Firstly, our analysis is based on only four RCTs, and more RCTs with a large sample size should be conducted to explore this issue. Next, there is significant heterogeneity, and no heterogeneity remains after excluding the study. This heterogeneity may be caused by different combination and methods of intra-articular fentanyl supplementation. Finally, various pain intensities caused by different procedures and operation time during knee arthroscopy may lead to some bias.

Conclusion
Intra-articular fentanyl supplementation does benefit in pain control after knee arthroscopy.

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