The efficacy of ketamine supplementation on pain management for knee arthroscopy

A meta-analysis of randomized controlled trials

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Abstract

Introduction: The efficacy of ketamine supplementation on pain management for knee arthroscopy remains controversial. We conduct a systematic review and meta-analysis to explore the influence of ketamine supplementation for knee arthroscopy.

Methods: We search PubMed, Embase, Web of Science, EBSCO, and Cochrane library databases through October 2018 for randomized controlled trials (RCTs) assessing the effect of ketamine supplementation on pain control for knee arthroscopy. This meta-analysis is performed using the random-effect model.

Results: Seven RCTs involving 300 patients are included in the meta-analysis. Overall, compared with control group for knee arthroscopy, ketamine supplementation reveals favorable impact on pain scores (mean difference [MD] = −2.95; 95% confidence interval [CI] = −3.36 to −2.54; P < 0.00001), analgesic consumption (standard mean difference [SMD] = −1.03; 95% CI = −1.70 to −0.36; P = .002), time to first analgesic requirement (Std. MD = 1.21; 95% CI = 0.45–1.96; P = .002) and malondialdehyde (Std. MD = −0.63; 95% CI = −1.05 to 3.10; P = .20), and shows no increase in nausea and vomiting (RR = 1.87; 95% CI = 0.66–3.10; P = .003).

Conclusions: Ketamine supplementation benefits to pain management and may reduce ischemia reperfusion injury in patients with knee arthroscopy.

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

Keywords: ketamine supplementation, knee arthroscopy, meta-analysis, pain management, randomized controlled trials

1. Introduction

Postoperative pain widely occurs in patients undergoing knee arthroscopy, and has become one of the main causes of delayed discharge and rehabilitation.[1–3] Many methods have been developed to prevent or treat pain following arthroscopic knee surgery, and they include systemic opioid and non-opioid analgesics, central and peripheral nerve blocks, preemptive analgesia, and intraarticular drug administration.[4–6] The duration of analgesia is typically short, and the use of combined drugs has increased progressively and holds important promise for pain relief after knee arthroscopy.[7,8]

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).[18]

2.1. Search strategy and study selection

Different drugs can act in synergy and the side effects of a single drug with high dose can be reduced or avoided.[9,10] For instance, dexamethasone added to ropivacaine is found to increase the duration of analgesia of an interscalene block from an average of 11.8 to 22.2 hours[11] and this prolonged analgesia of perineural dexamethasone may be caused by the direct action on the nerve or through systemic absorption.[12,13] Ketamine is known as an analgesic and anesthetic agent which has peripheral analgesic effects on pain and hyperalgesia with a variable duration.[14] Many studies have confirmed the efficacy of ketamine and levobupivacaine combination for pain relief in arthroscopic surgery.[5,6]

However, the efficacy of ketamine supplementation for knee arthroscopy has not been well established. Recently, several studies on the topic have been published, and the results have been conflicting.[14–17] With accumulating evidence, we therefore perform a systematic review and meta-analysis of RCTs to compare the efficacy of ketamine supplementation versus placebo for knee arthroscopy.
electronic search strategy is conducted using the following keywords ketamine, and knee 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: population: patients undergoing knee arthroscopy; intervention: ketamine supplementation; comparison: placebo; study design: RCT.

2.2. Data extraction and outcome measures
We have extracted the following information: author, number of patients, age, women, weight or body mass index, American Society of Anesthesiologists (ASA), and detail methods in each group etc. Data have been extracted independently by 2 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 within 2 hours. Secondary outcomes include analgesic consumption, time to first analgesic requirement, malondialdehyde, 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), 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 (Std. MD) or mean difference (MD) with 95% confidence interval (CI) for continuous outcomes (pain scores within 2 hours, analgesic consumption, time to first analgesic requirement, and malondialdehyde) risk ratios (RRs) with 95% CIs for dichotomous outcomes (nausea and vomiting). A 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 1 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. Five hundred twenty one potentially relevant articles are
Table 1

| No. | Author          | Year | Age (years) | Female (n) | Weight (kg) | ASA I/II (n) | Methods                                                                 | Body mass index (kg/m²) or weight (kg) | Jada scores |
|-----|-----------------|------|-------------|------------|-------------|--------------|-------------------------------------------------------------------------|----------------------------------------|-------------|
| 1   | Isik 2015       | 2015 | 20          | 38.6       | 11.5        | 26.6         | 4.1                                                                    | 11.5                                   | 26.6        |
| 2   | Gogus 2014      | 2014 | 30          | 44.6       | 13.9        | 24.7         | 8.7                                                                    | 15.9                                   | 34.3        |
| 3   | Ayoglu 2010     | 2010 | 20          | 40.9       | 2.7         | 20.3         | 5                                                                      | 2.7                                    | 24.7        |
| 4   | Cagla 2009      | 2009 | 20          | 16         | –           | 97           | 4.9                                                                    | –                                      | –           |
| 5   | Saricaoglu 2005 | 2005 | 15          | 31          | 4.7         | 31.0         | 60                                                                     | 4.7                                    | 4.0         |
| 6   | Batra 2005      | 2005 | 25          | 35          | 4.4         | 35.0         | 12                                                                     | 4.4                                    | 35.0        |
| 7   | Menigaux 2001   | 2001 | 25          | 37          | 2.7         | 37.0         | 13                                                                     | 2.7                                    | 37.0        |

ASA = American Society of Anesthesiologists.

3.2. Primary outcome: pain scores within 2 hours

This outcome data is analyzed with the random-effects model, and compared with control group for knee arthroscopy, ketamine supplementation exerts positive influence on pain scores within 2 hours (MD = −2.95; 95% CI = −3.36 to −2.54; P < .00001), with no heterogeneity among the studies (I² = 0%, heterogeneity P = .48) (Fig. 2).

3.3. Sensitivity analysis

No heterogeneity is observed among the included studies for pain scores within 2 hours, and thus 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 knee arthroscopy, ketamine supplementation is associated with significantly reduced analgesic consumption (Std. MD = −1.03; 95% CI = −1.70 to −0.36; P = .002; Fig. 3), increased time to first analgesic requirement (Std. MD = 1.21; 95% CI = 0.43−1.96; P = .002; Fig. 4), and decreased malondialdehyde (Std. MD = −0.63; 95% CI = −1.05 to 3.10; P = .20; Fig. 5). The incidence of nausea and vomiting shows no statistical difference between 2 groups (RR = 1.87; 95% CI = 0.65−3.10; P = .003; Fig. 6).

4. Discussion

Many factors can cause postoperative pain after arthroscopic surgery, and pain intensity is determined by the operation procedures. For instance, arthroscopic anterior cruciate ligament reconstruction and meniscus repair result in postoperative pain at different levels. The relief in postoperative pain is crucial for early postoperative rehabilitation and prevention of potential complications. Many anesthetic agents (e.g., opioids, ketamine, and clonidine) have been utilized alone or as adjuvant agents for pain control after arthroscopic knee surgery. When intraarticular drugs are applied alone, their time of effect is short, and increased utilization of drug combinations may amplify the analgesic effect.

Ketamine acts through interacting with many receptors such as N-methyl-D-aspartate (NMDAr), serotonergic, and adrenergic receptors, which exhibit important roles in analgesia. NMDAr is located in the peripheral and somatic pain pathways, and it has an...
important role in nociception. Ketamine has been applied either alone or as an intraarticular adjuvant. Several studies have confirmed the efficacy of intraarticular ketamine in postoperative pain treatment after arthroscopic knee surgery, whereas the conflicting results are observed in another study. Our meta-analysis concludes that ketamine supplementation is associated with remarkably reduced pain scores within 2 hours, analgesic consumption, and prolonged time to first analgesic requirement for knee arthroscopy.

After the tourniquet is released, excessive formation of reactive oxygen species leads to peroxidation of membrane lipids during ischemia reperfusion injury, which subsequently stimulates oxidation of the polyunsaturated fatty acids, destroying membrane structures and producing toxic metabolites such as malondialdehyde. Malondialdehyde in ketamine supplementation group is substantially lower than that in control group for knee arthroscopy based on the results of our meta-analysis, suggesting the potential of ketamine supplementation group in alleviating

| Study or Subgroup | Ketamine group | Control group | Mean Difference | IV, Random, 95% CI |
|-------------------|----------------|---------------|----------------|-------------------|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | Mean Difference | IV, Random, 95% CI |
| Ayoglu 2010       | 2.2 | 0.6 | 15  | 2.1 | 0.6 | 15  | 90.6% | -2.50 [-3.83, -1.17] |
| Sarcaooglu 2005   | 3.6 | 0.8 | 15  | 3.0 | 0.6 | 15  | 90.6% | -3.00 [-4.34, -1.67] |
| Total (95% CI)    | 35  | 100% | 35  | 100% | 35  | 100% | 90.6% | -2.50 [-3.83, -1.17] |
| Heterogeneity: $\text{tau}^2 = 0.00; \text{chi}^2 = 0.49; df = 1 (P = 0.48); I^2 = 0%$ | Test for overall effect: $Z = 14.16 (P < 0.00001)$ | |

Figure 2. Forest plot for the meta-analysis of pain scores within 2 hours.

| Study or Subgroup | Ketamine group | Control group | Std. Mean Difference | IV, Random, 95% CI |
|-------------------|----------------|---------------|----------------------|-------------------|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | Std. Mean Difference | IV, Random, 95% CI |
| Ayoglu 2010       | 5.8  | 2.6 | 20    | 10.7 | 5.1 | 20    | 33.2% | -1.19 [-1.86, -0.51] |
| Bata 2005         | 3.5  | 0.8 | 20    | 3.9  | 0.9 | 20    | 34.9% | -0.41 [-1.04, 0.21] |
| Cagla 2009        | 22.6 | 6.2 | 20    | 36.5 | 11.2| 20    | 31.9% | -1.55 [-2.26, -0.83] |
| Total (95% CI)    | 60  | 100% | 60  | 100% | 60  | 100% | 31.9% | -1.03 [-1.70, -0.36] |
| Heterogeneity: $\text{tau}^2 = 0.23; \text{chi}^2 = 5.93; df = 2 (P = 0.05); I^2 = 66%$ | Test for overall effect: $Z = 3.03 (P = 0.002)$ | |

Figure 3. Forest plot for the meta-analysis of analgesic consumption.

| Study or Subgroup | Ketamine group | Control group | Std. Mean Difference | IV, Random, 95% CI |
|-------------------|----------------|---------------|----------------------|-------------------|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | Std. Mean Difference | IV, Random, 95% CI |
| Batra 2005        | 5.7  | 0.8 | 20    | 5.1  | 1.1 | 20    | 35.9% | 0.61 [-0.02, 1.25] |
| Cagla 2009        | 198 | 21  | 20    | 136 | 20 | 20    | 32.4% | 1.90 [1.14, 2.66] |
| Sarcaooglu 2005   | 60  | 18 | 15    | 40  | 15 | 15    | 31.7% | 1.17 [0.39, 1.96] |
| Total (95% CI)    | 55  | 100% | 55  | 100% | 55  | 100% | 31.7% | 1.21 [0.45, 1.96] |
| Heterogeneity: $\text{tau}^2 = 0.31; \text{chi}^2 = 6.53; df = 2 (P = 0.04); I^2 = 69%$ | Test for overall effect: $Z = 3.13 (P = 0.002)$ | |

Figure 4. Forest plot for the meta-analysis of time to first analgesic requirement.

| Study or Subgroup | Ketamine group | Control group | Std. Mean Difference | IV, Random, 95% CI |
|-------------------|----------------|---------------|----------------------|-------------------|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | Std. Mean Difference | IV, Random, 95% CI |
| Gogus 2014        | 97.2 | 21.9 | 30    | 110.6 | 32 | 30    | 68.6% | -0.48 [-1.00, 0.03] |
| Sarcaooglu 2005   | 118.74 | 22.44 | 15    | 141.09 | 22.93 | 15    | 31.4% | -0.94 [-1.70, -0.18] |
| Total (95% CI)    | 45  | 100% | 45  | 100% | 45  | 100% | 31.4% | -0.63 [-1.05, -0.20] |
| Heterogeneity: $\text{tau}^2 = 0.00; \text{chi}^2 = 0.95; df = 1 (P = 0.33); I^2 = 0%$ | Test for overall effect: $Z = 2.86 (P = 0.004)$ | |

Figure 5. Forest plot for the meta-analysis of malondialdehyde.

| Study or Subgroup | Ketamine group | Control group | Risk Ratio | M-H, Random, 95% CI |
|-------------------|----------------|---------------|------------|---------------------|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | Risk Ratio | M-H, Random, 95% CI |
| Ayoglu 2010       | 2.2 | 0.6 | 15  | 2.1 | 0.6 | 15  | 90.6% | 0.86 [0.33, 2.25] |
| Isik 2015         | 1.0 | 0.2 | 20  | 2.0 | 0.2 | 20  | 90.6% | 0.50 [0.05, 5.08] |
| Total (95% CI)    | 50  | 100% | 50  | 100% | 50  | 100% | 90.6% | 0.79 [0.32, 1.93] |
| Heterogeneity: $\text{tau}^2 = 0.00; \text{chi}^2 = 0.18; df = 1 (P = 0.67); I^2 = 0%$ | Risk Ratio = 0.51 (P = 0.51) | |

Figure 6. Forest plot for the meta-analysis of nausea and vomiting.
ischemia reperfusion injury. There is no significant difference of nausea and vomiting between 2 groups. Regarding the sensitivity analysis, although there is no significant heterogeneity, several factors may have some effect on the pooling results. They mainly include different doses, routes and combination of ketamine supplementation, as well as various operation procedures etc.

This meta-analysis has several potential limitations. Firstly, our analysis is based on 7 RCTs, and all of them have a relatively small sample size (n < 100). These may lead to overestimation of the treatment effect in smaller trials. More RCTs with large sample size should be conducted to explore this issue. Next, various doses, routes, and combination of ketamine supplementation are included in this meta-analysis, which may have some impact on the pooling results. Finally, different operation procedures are performed for knee arthroscopy, and may also affect the pooled results.

5. Conclusions
Ketamine supplementation exhibits additional benefits for pain control in patients with knee arthroscopy.

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Conceptualization: Linlin Pan, Teng Ma.
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