International Journal of Surgery 70 (2019) 70–83

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.elsevier.com/locate/ijsu

Review

Ketamine reduces pain and opioid consumption after total knee arthroplasty: A meta-analysis of randomized controlled studies

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ARTICLE INFO

Keywords:
Total knee arthroplasty
Ketamine
Pain
Opioid
Meta-analysis

ABSTRACT

Objective: To examine the analgesic efficacy and safety of ketamine after total knee arthroplasty.

Methods: We searched for all articles on ketamine in patients with total knee arthroplasty in electronic databases, including PubMed, Embase, Ovid, Cochrane Library, Web of Science, CNKI, Wanfang Data, and VIP, up to the February 2019. Randomized controlled trials comparing ketamine and the placebo for pain management after total knee arthroplasty were utilized. The outcome measurements consist of the pain score, opioid consumption, length of hospitalization and postoperative complications. All data analyses were conducted using STATA 13.0. Cochrane Collaboration's tool was adopted to assess the risk of bias.

Results: A total of six randomized controlled trials were included in the meta-analysis. The present meta-analysis demonstratedpt that there were significant differences between the two groups regarding the pain score within the first 24 postoperative hours. Ketamine was associated with a significant reduction of cumulative morphine consumption. Notably, ketamine could significantly decrease the incidence of nausea and vomiting without increasing the risk of thrombosis.

Conclusion: Ketamine is effective in reducing pain and cumulative morphine consumption during the early postoperative period after total knee arthroplasty. In addition, the use of ketamine is associated with a lower incidence of adverse effects.

1. Introduction

Total knee arthroplasty (TKA) is a successful surgical procedure to treat end-stage osteoarthritis (OA) and rheumatoid arthritis (RA) [1,2]. It has been reported that approximately 300 thousand TKAs were operated annually in the U.S and the incidence was on the rise along with the aging process [3]. TKA has been a serious social problems. However, TKA is also related with postoperative pain ranging from moderate to severe, which may delay functional recovery, while increasing the risk of thrombotic complications, such as deep venous thrombosis (DVT) and pulmonary embolism (PE) [4,5]. Additionally, prolonged duration of hospitalization may increase more medical expenses. Therefore, pain management after TKA is an important issue for surgeons and patients to recognize.

Although various effective interventions including femoral nerve block, peri-articular injection, adductor canal block, non-steroid anti-inflammatory drug, and epidural morphine have been used for pain control after TKA [6–10], the optimal analgesia still remains a subject of debate. Recently, the use of ketamine has been popularized in the surgical field and exhibits improved outcomes for analgesia. Ketamine is a non-competitive N-methyl-D-aspartate receptor antagonist, which is widely used in perioperative anesthesia for its analgesic efficacy and stable effect on the cardiovascular system [11]. Published articles have demonstrated that ketamine played an important role as an additive to multimodal analgesia post-operation. Zhu et al. [12] reported that intravenous ketamine infusion significantly reduced postoperative pain scores and opioid consumption after laparoscopic cholecystectomy.

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https://doi.org/10.1016/j.ijsu.2019.08.026
Received 2 April 2019; Received in revised form 25 July 2019; Accepted 21 August 2019
Available online 22 August 2019

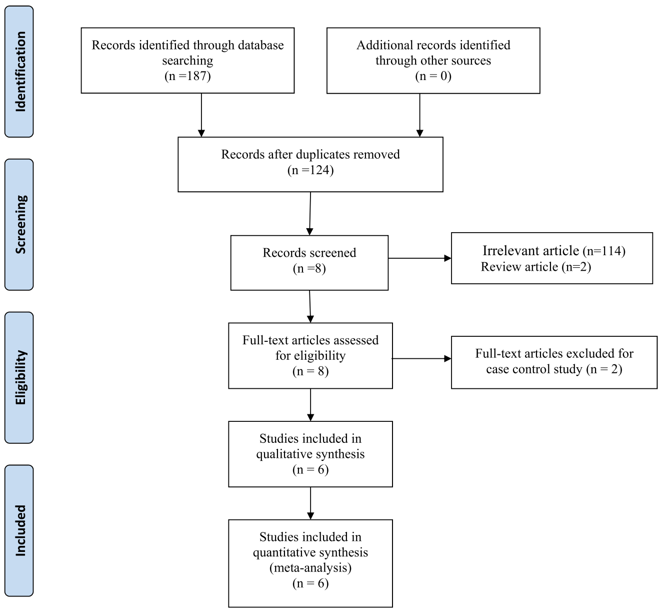


Fig. 1. Flow chart of study selection.

Although numerous previous trials have assessed ketamine's role in postoperative analgesia, there is no definite analgesic effect of ketamine in TKA because there are limited published studies. Therefore, we performed a systematic review and meta-analysis from randomized controlled trials (RCTs) to evaluate the efficacy and safety of ketamine for reducing pain after TKA. We hypothesized that ketamine acted as an effective analgesic after TKA without increasing the incidence of adverse effects.

2. Methods

This meta-analysis was performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist [13] and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines. No ethical approval was required.

2.1. Literature search

We searched for all articles regarding ketamine in TKA patients in electronic databases, including PubMed, Embase, Ovid, Cochrane Library, Web of Science, CNKI, Wanfang Data, and VIP, up to the February 2019 period. In addition, a manual search of the bibliographies of identified articles was also performed as a means to identify potentially relevant studies. A structured search was performed using the following search string: (ketamine [Mesh Terms]) AND (TKA OR TKR OR total knee arthroplasty OR total knee replacement [Title/Abstract]). Our search did not include language restrictions.

2.2. Inclusion and exclusion criteria

Studies were chosen for meta-analysis if they met the following criteria: Population: patients with knee osteoarthritis scheduled for TKA. Intervention: TKA with ketamine for pain management. Comparison: TKA without ketamine. Outcomes: postoperative pain score at 6–48 h, morphine consumption, length of hospitalization and adverse effects. Study design: RCTs. Studies were excluded if any of the following existed: low-quality RCTs and non-RCTs, undefined sample and control sources, nontherapeutic clinical studies, nonoriginal studies, non-full-text reports, and undefined grouping.

2.3. Data extraction

The outcomes and characteristics of each included study were independently screened by two researchers. The mean and standard deviation (SD) of outcomes was extracted directly from articles. If not reported, it was estimated based on sample size, median and range. Data was also extracted from figures utilizing GetData V.2.20. The following background information was extracted from the included studies: first author's name, year of publication, mean age, gender, sample size, doses of ketamine, and follow-up time point. Postoperative pain score and cumulative morphine consumption were chosen as the primary outcome in this meta-analysis. Secondary outcome measures included the length of hospitalization and adverse effects.

2.4. Quality assessment

Two authors independently assessed the methodological quality of the included studies through using of the Cochrane collaboration's tool for assessing the risk of bias. It is a two-part tool, addressing seven specific domains, including sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. The judgment of each reviewer on each domain was categorized as ‘low risk,’ ‘high risk,’ or ‘unclear risk’ of bias. Recommendations Assessment, Development and Evaluation (GRADE) system was used to grading the evidence level. Any disagreement was settled by a group discussion with the group mentor.

2.5. Statistical analysis

All data analyses were conducted using STATA 13.0. For continuous outcomes, each character was calculated using the weighted mean difference (WMD). Relative risk (RR) was calculated for dichotomous outcomes and the data of the included study was measured by 95%

Table 1
Characteristics of the included RCTs.

Study	Year	Design	Study	No. of patients	Gender (Male)	Age	Doses of ketamine	Outcomes	Follow up
				Ketamine Placebo	Ketamine Placebo	Ketamine Placebo			
Adam et al.	2005	RCT	TKA	20 20	13 14	68 69	Intravenous 3 μg/kg/min until the patient emerged from anesthesia, and then 1.5 μg/kg/min maintained for 48 h	VAS at 6 h, VAS at 12 h VAS at 24 h opioid consumption 48 h	3 months
Aveline et al.	2009	RCT	TKA	25 24	15 15	72 70	Intravenous 0.2 mg/kg followed by a continuous infusion at 120 μg/kg/h until the end of surgery, and then 60 μg/kg/h until the second postoperative day	VAS at 6 h, VAS at 12 h VAS at 24 h, VAS at 48 h opioid consumption 24 h opioid consumption 48 h duration of hospitalization complication	6 weeks
Perrin et al.	2009	RCT	TKA	5 7	3 4	66 60	Intravenous 0.5 mg/kg bolus followed by 4 μg/kg/min infusion	VAS at 6 h, VAS at 12 h VAS at 24 h, VAS at 48 h opioid consumption 24 h duration of hospitalization	26 weeks
Sobrinho et al.	2012	RCT	TKA	19 20	16 14	67 67	Intra-articular 0.25 mg/kg	VAS at 6 h, VAS at 12 h VAS at 24 h duration of hospitalization complication	No mentioned
Cengiz et al.	2014	RCT	TKA	30 30	25 19	58 59	Intravenous 6 μg/kg/minute	VAS at 6 h, VAS at 12 h VAS at 24 h opioid consumption 24 h opioid consumption 48 h duration of hospitalization complication	6 months
Zhang et al.	2018	RCT	TKA	21 23	15 16	56 54	Intra-articular 2 mg/kg	VAS at 6 h, VAS at 12 h VAS at 24 h, VAS at 48 h opioid consumption 24 h opioid consumption 48 h complication	1 month

RCT: randomized controlled trial, TKA: total knee arthroplasty, VAS: visual analogue scale.

Table 2
Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Adam 2005	+	+	+	?	+	+	+
Aveline 2009	+	+	+	?	+	+	+
Cengiz 2014	+	?	+	+	+	+	+
Perrin 2009	+	?	+	+	+	+	+
Sobrinho 2012	+	+	?	?	+	+	+
Zhang 2018	+	?	+	?	+	+	+

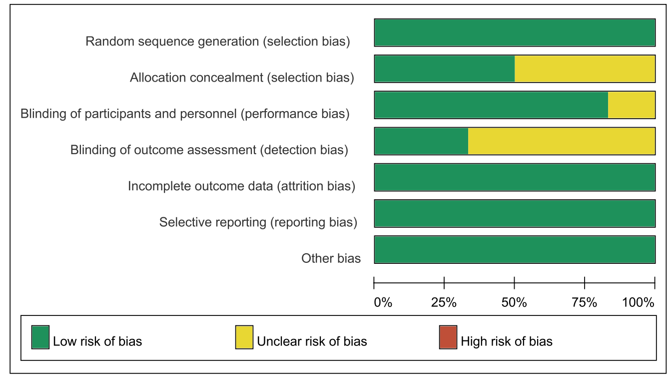
confidence intervals (CIs). Heterogeneity was examined using the I^2 statistic. Studies with an I^2 of 25%–50% were considered to possess low heterogeneity, and a fixed effect model was used. $I^2 > 50\%$ was considered to be of a high heterogeneity, and a random effect model was used. If needed, a subgroup analysis was conducted. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Search results

Fig. 1 depicts a flowchart that describes the process of screening and

Table 3
Risk of bias graph.



selecting trials. Our initial search yielded a total of 187 relevant articles; those of which 63 were excluded for duplicate studies and various reasons on the basis of the titles and abstracts. 114 were excluded for irrelevant articles and 4 was excluded because of case control and review article. In addition, manual search of relevant reference did not identify any additional studies. Finally, six RCTs [14–19] were selected for this meta-analysis.

3.2. Studies characteristics

Descriptive data for the studies in this systematic review and meta-analysis are reflected in Table 1. The six studies were published between the 2005 and 2018 period, and included 244 participants who were diagnosed with knee osteoarthritis in all trials. The mean age ranged from 54 to 72 years. 120 patients received intravenous or intra-articular ketamine for postoperative pain control and 124 patients received the placebo. The duration of follow up ranged from 4 to 26 weeks.

3.3. Quality assessment

Table 2 and Table 3 summarized the risk of the bias assessment summary and the risk of bias graph respectively. The methodological quality of the six RCTs were evaluated with Cochrane Collaboration's tool. All RCTs indicated that participants were randomized with a computerized random number generator. Three RCTs reported that an opaque, sealed envelope was used to ensure allocate concealment. Five studies reported the blinding of the participant and personnel. All RCTs provided complete outcome data.

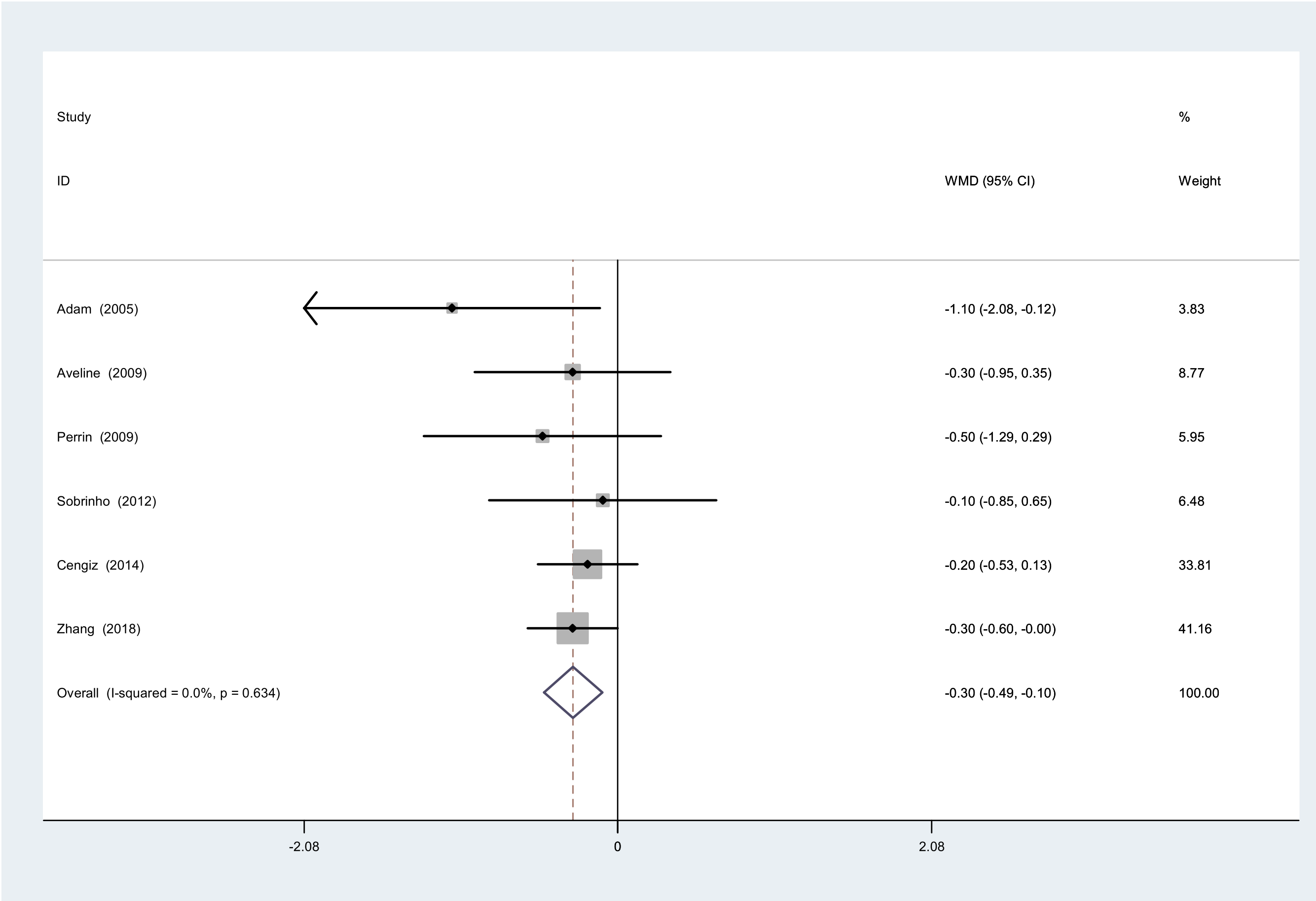


Fig. 2. Forest plot diagram of postoperative pain score at 6 h.

3.4. Primary outcome

3.4.1. Pain score at 6 h

Six RCTs reported the outcome of visual analogue scale (VAS) at 6 h after TKA. There was no significant heterogeneity among studies ($I^2 = 0\%$, $p = 0.63$) and a fixed effect model was applied. The pooled data showed that ketamine demonstrated a significantly lower pain score than compared with the placebo (WMD: −0.296; 95% CI: −0.488 to −0.104; p = 0.003, Fig. 2).

3.4.2. Pain score at 12 h

Six studies reported VAS at 12 h after TKA. A fixed-effects model was applied ($I^2 = 0\%$, $p = 0.57$). Significant differences were identified between the two groups regarding VAS at 12 h after TKA (WMD: −0.304; 95% CI: −0.491 to −0.117; p = 0.001, Fig. 3).

3.4.3. Pain score at 24 h

A total of six RCTs showed the VAS at 24 h after TKA. There was significant heterogeneity and a random effect model was adopted ($P = 0.004$, $I^2 = 71.4\%$). Our meta-analysis demonstrated that there existed significant difference between groups regarding the VAS at 24 h (WMD: −0.252; 95% CI: −0.404 to −0.101; p = 0.001, Fig. 4).

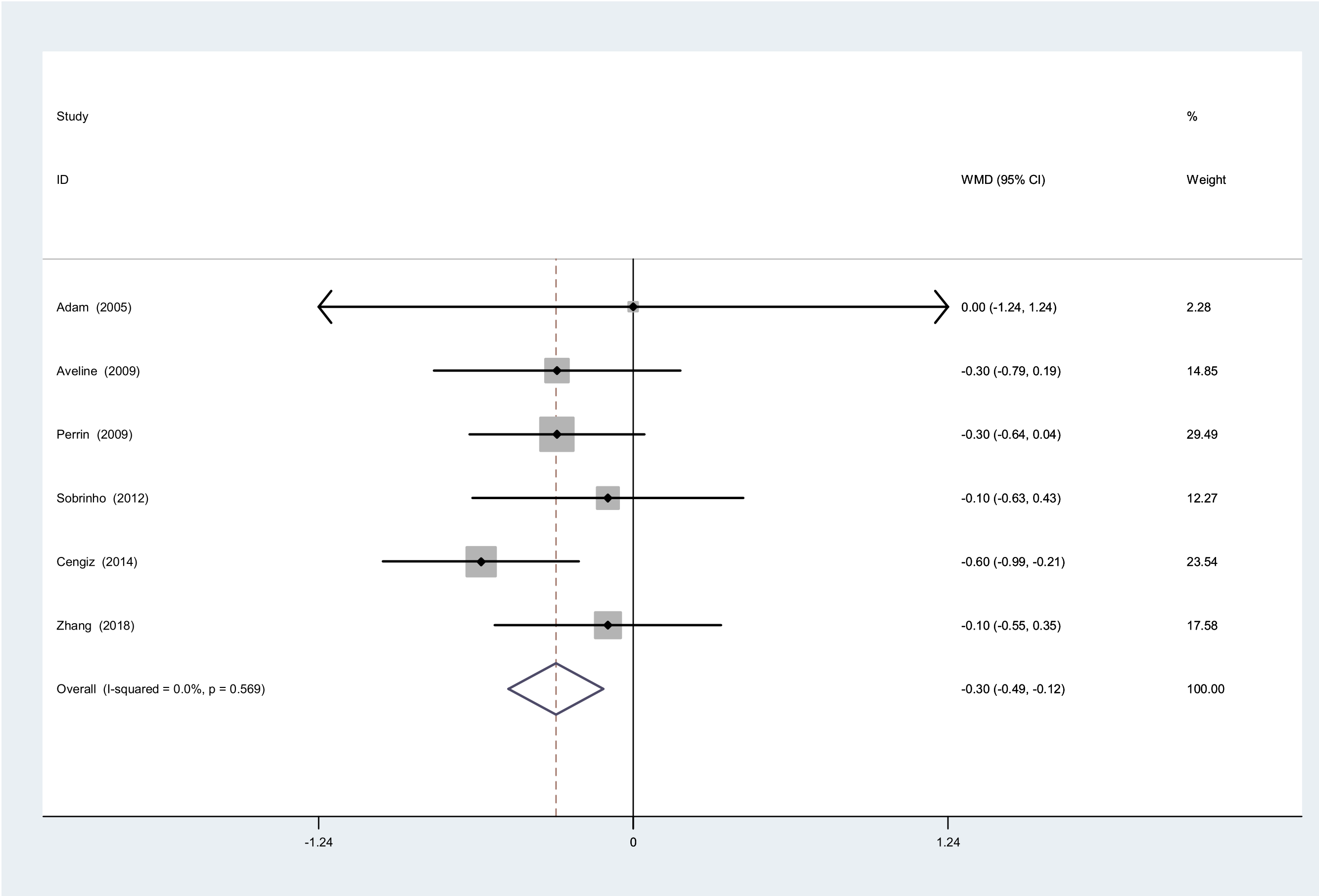


Fig. 3. Forest plot diagram of postoperative pain score at 12 h.

3.4.4. Pain score at 48 h

VAS at 48 h after TKA was assessed in three RCTs. Pooled analysis revealed no significant difference in the VAS at 48 h (WMD: −0.007; 95% CI: −0.131 to 0.116; p = 0.911, Fig. 5).

3.4.5. Cumulative morphine consumption at 24 h

Four studies demonstrated the outcome of cumulative morphine consumption at 24 h after TKA. No significant heterogeneity was found (I^2 = 98.2%, p < 0.001) and a random effect model was used. The combined data indicated that the cumulative morphine consumption in the ketamine group was significantly lower in the control group (WMD: −17.402; 95% CI: −34.006 to −0.798; p = 0.040, Fig. 6).

3.4.6. Cumulative morphine consumption at 48 h

Four RCTs reported the cumulative morphine consumption at 48 h after TKA. There was significant heterogeneity between studies (I^2 = 96.8%, p < 0.001) and a random effect model was adopted. A significant decrease in cumulative morphine consumption at 48 h was observed in the ketamine group compared with the control group (WMD: −19.963; 95% CI: −34.056 to −5.871; p = 0.005, Fig. 7).

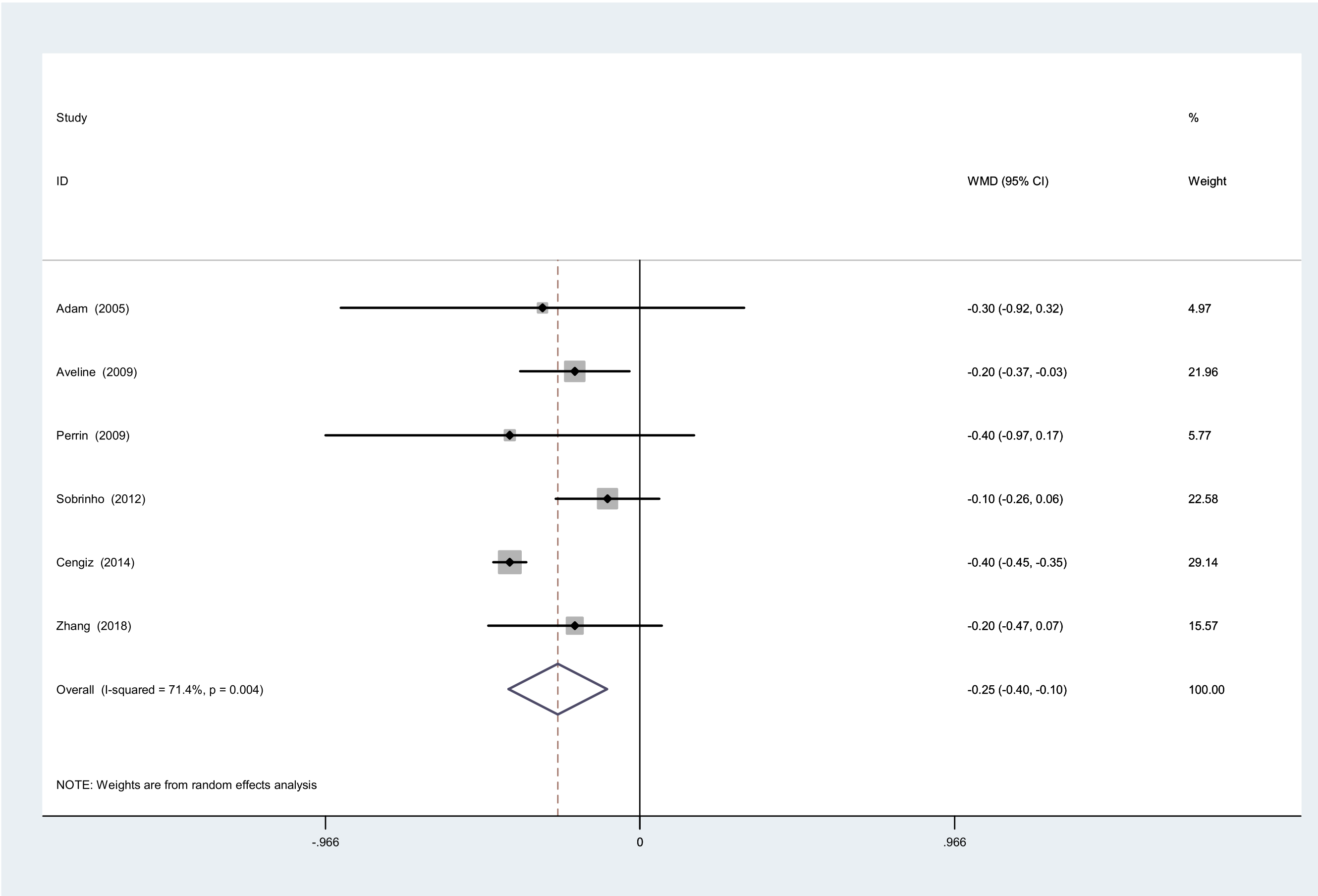


Fig. 4. Forest plot diagram of postoperative pain score at 24 h.

3.5. Secondary outcome

3.5.1. Duration of hospitalization

Length of hospitalization was reported in four articles. A fixed effect model was utilized ($I^2 = 0\%$, $p = 0.709$). Pooled analysis revealed that there was no significant difference between groups in length of hospitalization (WMD: 0.070; 95% CI: −0.314 to 0.453; p = 0.722, Fig. 8).

3.5.2. Complications

Four studies reported postoperative complications such as nausea, vomiting, DVT and PE. The present meta-analysis indicated that the use of ketamine could significantly reduce the incidence of nausea and vomiting without increasing the risk of thrombosis (Fig. 9).

3.6. Evidence level

GRADE system was adopted to assess the evidence level. The overall evidence was moderate, which indicated that further research was likely to significantly alter confidence in the effect estimate and may change the estimate (Table 4).

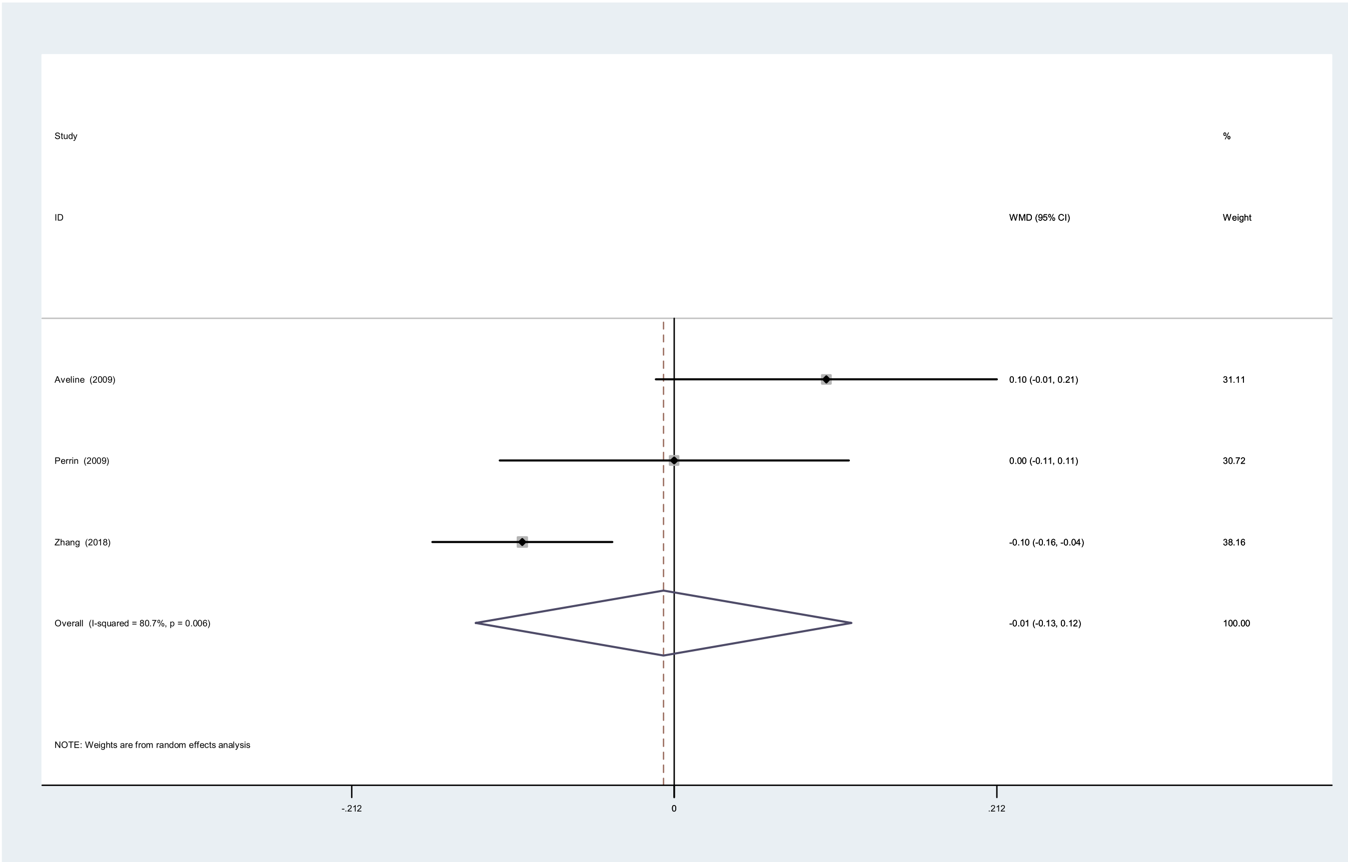


Fig. 5. Forest plot diagram of postoperative pain score at 48 h.

3.7. Sensitivity analysis

Sensitivity analysis was conducted by omitting one paper at a time and calculating the pooled outcomes for the remaining articles. After excluding the study of Cengiz et al., there was no significant heterogeneity among studies (Fig. 10). Pooled analysis revealed that significant differences still remained between groups in their pain scores at 24 h.

4. Discussion

This was the first meta-analysis that included sporadic information related to the comparison between ketamine and the placebo for postoperative pain treatment after TKA. The most interesting finding was that the use of ketamine was effective in reducing pain and cumulative morphine consumption during the early post-operative period after TKA. In addition, the use of ketamine was associated with a lower incidence of adverse effects.

Osteoarthritis (OA) is the most common joint disease worldwide [20]. It is a slowly progressive, disabling joint disorder affecting people's quality of life. More than 700,000 total knee replacements are performed annually in the U.S [21]. There is an urgent necessity to identify effective perioperative pain management in which the final TKA outcome satisfies surgeons. OA has been and is becoming a serious public health issue. Inadequate pain control after TKA would increase the consumption of rescued opioid, disrupt sleep, influence

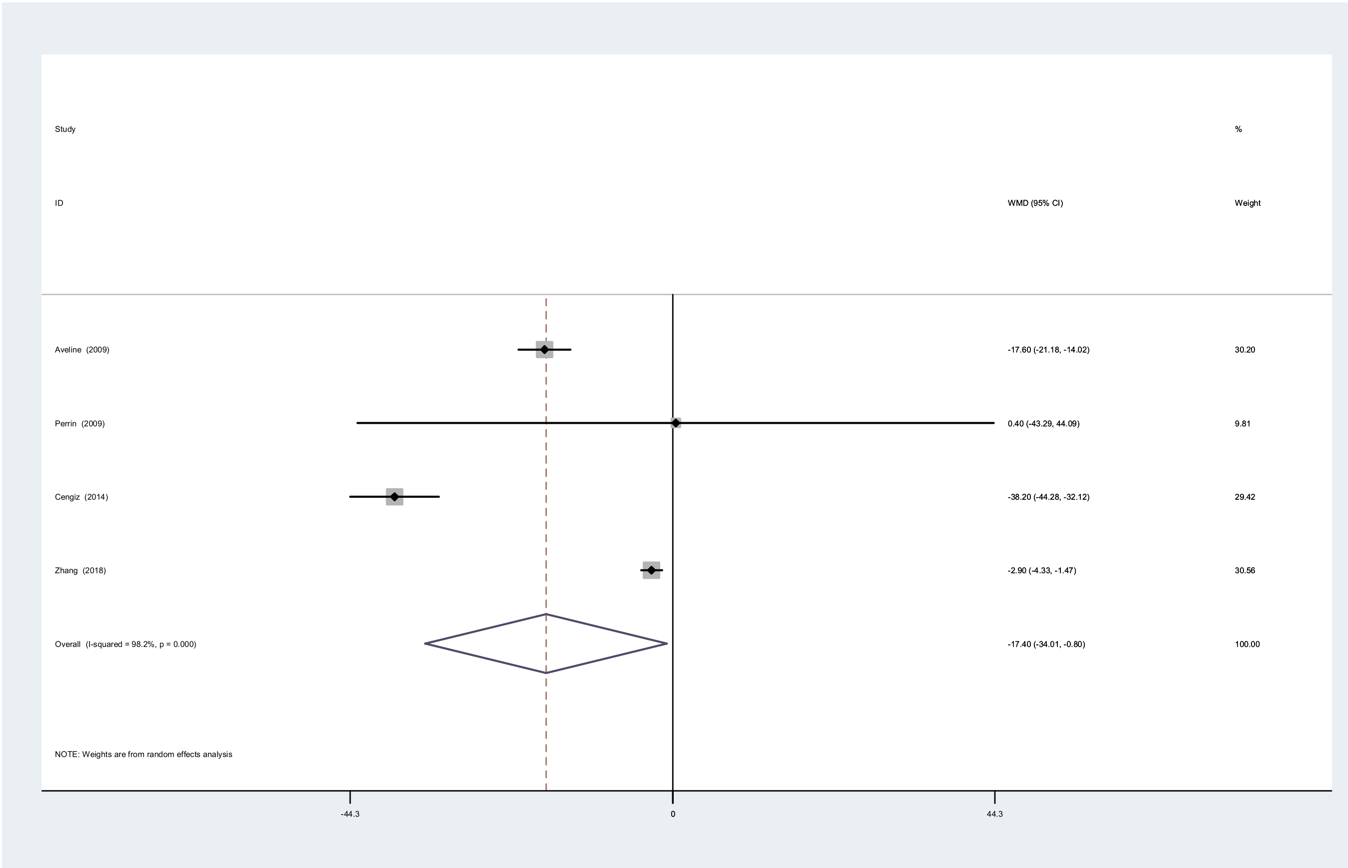


Fig. 6. Forest plot diagram of cumulative morphine consumption at 24 h.

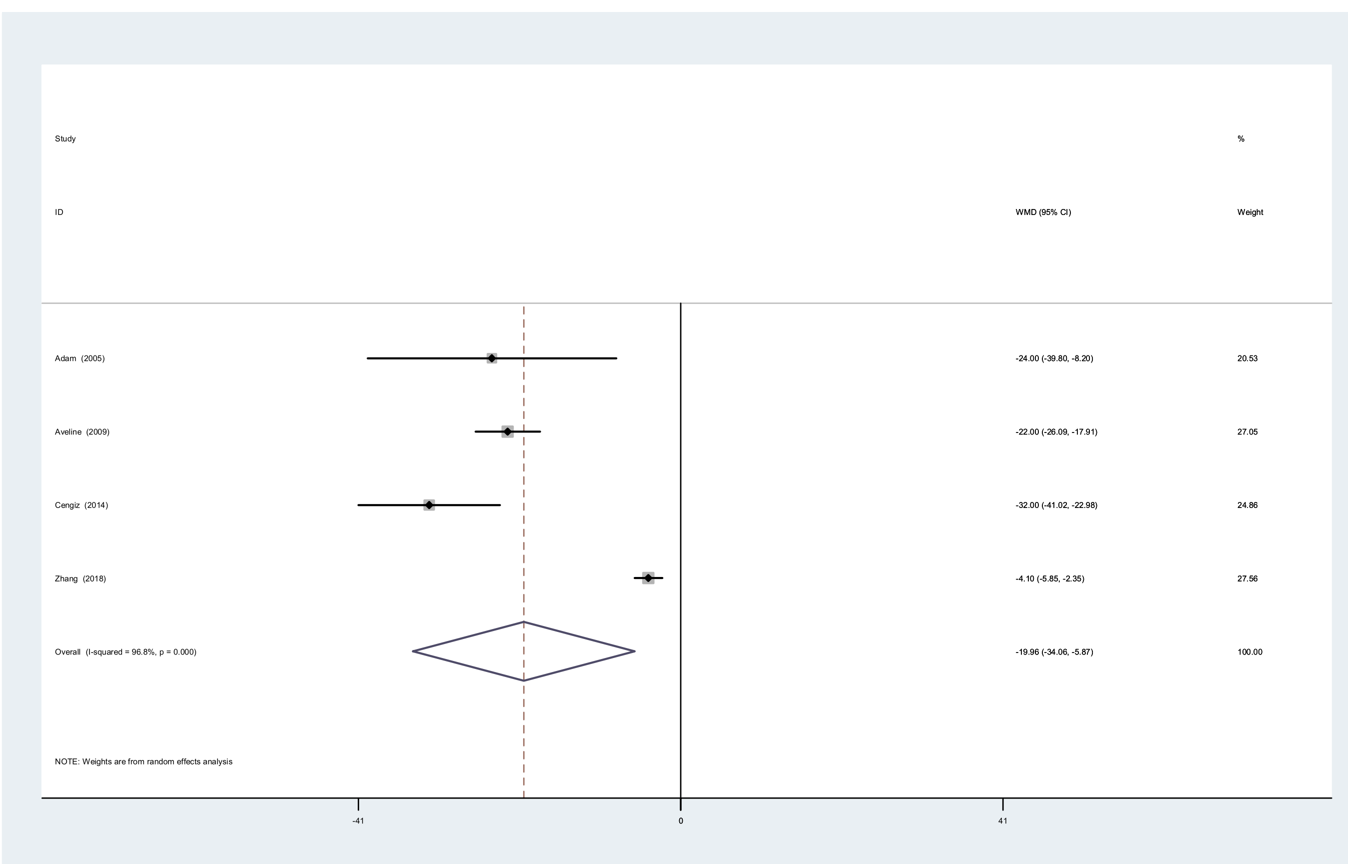


Fig. 7. Forest plot diagram of cumulative morphine consumption at 48 h.

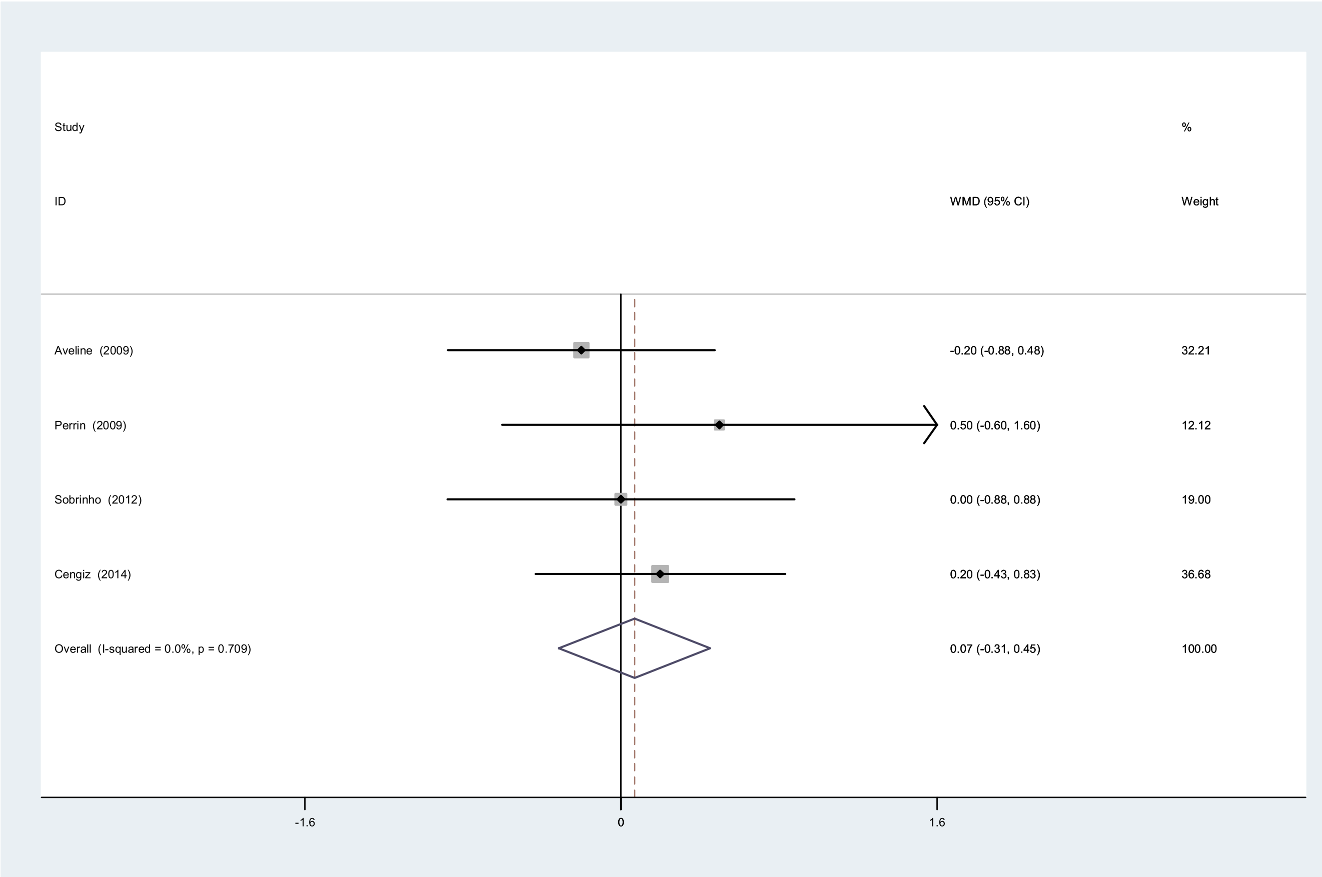


Fig. 8. Forest plot diagram of duration of hospitalization.

physical exercise, while increasing the length and total cost of hospital stay.

Among the various methods, the intravenous analgesic method have been confirmed to be safe and effective in postoperative pain management after TKA. The efficacy of ketamine administration for postoperative pain relief has been examined and debated for decades, but the findings are still contradictory. Ketamine has been utilized for surgical procedures since the 1980s, with the purpose to act as a mono-anesthetic drugs with analgesia, unconsciousness, and stable properties. Previous studies have reflected an improved analgesic efficiency of ketamine in patients with post-operative pain. Singh et al. [22] reported that preemptive ketamine has a definitive role in reducing postoperative pain and analgesic requirement in patients undergoing laparoscopic cholecystectomy. Becke et al. [23] demonstrated that intraoperative low dose ketamine had no effect on pain relief and morphine consumption during the first 72 h after surgery. However, the subjects in these articles were not confined to TKA patients. Consequently, there was lack of reliable evidence regarding the definite efficacy of ketamine for pain management in TKA. In our study, six RCTs with 244 patients reported the outcome of pain score. VAS (0–10 cm) was used for pain measurement after TKA. The combined data showed that ketamine administration was associated with a significant reduction of VAS within the first 24 postoperative hours after TKA. However, there was no noticeable difference between groups regarding the VAS at 48 h. The lack of uniform administration of ketamine might contribute to the significant heterogeneity.

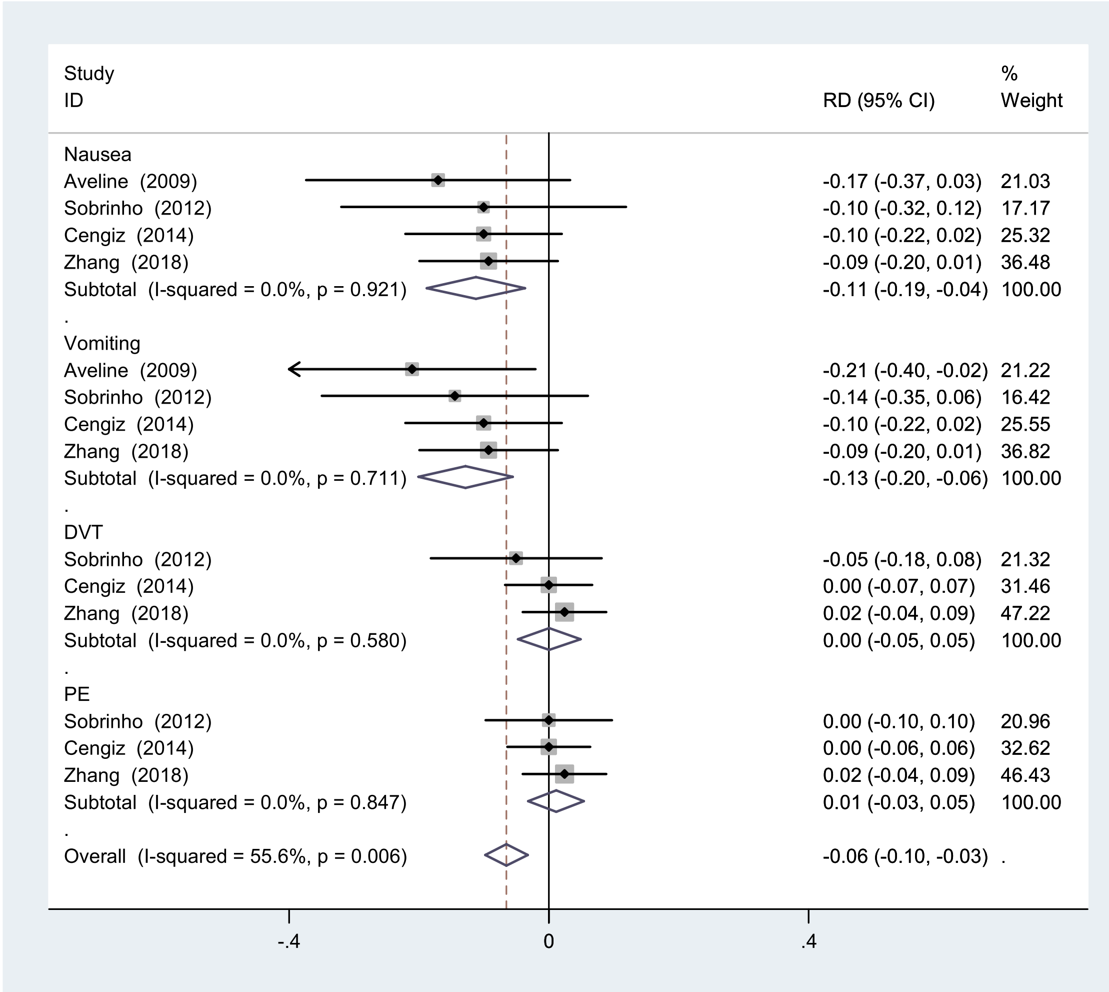


Fig. 9. Forest plot diagram of postoperative complications.

The occurrence of central sensitization, which can cause post-operative pain amplification, has been deemed as a risk factor for chronic pain after operation. Aveline et al. [15] reported that the prevalence of chronic pain was 12.5% in the ketamine group compared with 26.1% in the control group. According to a long-term follow-up, ketamine could also decrease the incidence of neuropathic pain and improve range of motion. Few included RCT reported the outcome of functional recovery and further investigation was necessary.

Postoperative pain management plays an important role in guaranteeing the final successful outcome of TKA. It was reported that approximately 30%–60% of patients suffered moderate to severe post-operative pain, especially during the early post-operative period after TKA [24]. Morphine, a mu-opioid receptor agonist, relieves pain by binding and activating the receptors in both the central and peripheral nervous systems [25]. However, the opioid has been associated with many adverse effects, such as, gastrointestinal reaction, headache, urinary retention, respiratory depression and constipation, which impeded the postoperative convalescence and prolonged duration of hospitalization [26,27]. Opioid dependence, a severe addictive disorder and major social problem, has been shown to be heritable. As a non-

Table 4
The GRADE evidence quality.

Quality assessment						Effect	Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision			
Pain score at 6 h								
6	RCT	no serious limitations	no serious inconsistency	no serious indirectness	no serious limitations	WMD: −0.296; 95% CI: −0.488 to −0.104	HIGH	CRITICAL
Pain score at 12 h								
6	RCT	no serious limitations	no serious inconsistency	no serious indirectness	no serious limitations	WMD: −0.304; 95% CI: −0.491 to −0.117	HIGH	CRITICAL
Pain score at 24 h								
6	RCT	no serious limitations	serious inconsistency	no serious indirectness	no serious limitations	WMD: −3.029; 95% CI: −5.119 to −0.939	MODERATE	CRITICAL
Pain score at 48 h								
3	RCT	no serious limitations	serious inconsistency	no serious indirectness	no serious limitations	WMD: −0.252; 95% CI: −0.404 to −0.101	MODERATE	CRITICAL
Cumulative morphine consumption at 24 h								
4	RCT	no serious limitations	no serious inconsistency	no serious indirectness	no serious limitations	WMD: −17.402; 95% CI: −34.006 to −0.798	HIGH	CRITICAL
Cumulative morphine consumption at 48 h								
4	RCT	no serious limitations	serious inconsistency	no serious indirectness	no serious limitations	WMD: −19.963; 95% CI: −34.056 to −5.871	MODERATE	CRITICAL
Duration of hospitalization								
4	RCT	no serious limitations	no serious inconsistency	no serious indirectness	no serious limitations	WMD: 0.070; 95% CI: −0.314 to 0.453	HIGH	CRITICAL

competitive N-methyl-D-aspartate receptor antagonist, ketamine was deemed to inhibit the sensitization of the nociceptive pathways, and to prevent the activation of the pronociceptive system associated with opiates as well as with opiate tolerance [28]. Theoretically, ketamine had a morphine-sparing during surgery. However, recent published articles reflected mixed results in TKA patients. Cengiz et al. [17] reported that ketamine resulted in less rescue analgesia, with longer time to first request. While, Perrin et al. [19] showed that there was no significant difference between groups. Our study first analyzed the cumulative morphine consumption between ketamine and the placebo, and demonstrated that patients in the ketamine group consumed significantly less morphine equivalents during the postoperative 24–48 h. Published articles have reported that intraoperative administration of ketamine (75–150 μg/kg) allowed up to a 55% reduction in postoperative morphine demand. Due to the small number of included RCTs, no dose-response analysis was performed and more RCTs were required.

As is widely known, opioid use is associated with numerous side effects. Therefore, the morphine-sparing effect of ketamine will hold less clinical value if the opioid-related side-effects cannot be mitigated. In the present meta-analysis, four studies provided the data of postoperative complications after TKA. The overall incidence of gastrointestinal reaction is 5/95 in ketamine groups compared with 18/97 in the control group. The use of ketamine results in a significant reduction of opioid-related side-effects. Notably, DVT and PE are severe complications which may cause death after major orthopedic surgery. No significant difference was identified regarding the incidence of thrombosis.

Several limitations of this study should be noted. Firstly, we only included six RCTs with 244 patients in our study; more RCTs with higher quality will be helpful for future study. Secondly, there existed significant heterogeneity among studies and the subgroup analysis was not performed due to the small number of included articles, thus the source of heterogeneity was not identified. Thirdly, having been restricted to a limited number of included studies and data extracted, we did not compare the functional recovery between the two groups. Lastly, the lack of uniform doses of ketamine and the start time of administration might contribute to the deviation of the overall results in the present study.

5. Conclusion

Ketamine is effective in reducing pain and cumulative morphine consumption during the early post-operative period after total knee arthroplasty. In addition, the use of ketamine is associated with a lower incidence of adverse effects.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data statement

I confirmed that the relevant data is real and you can get them by consulting correspondence author.

Conflicts of interest

All authors state that they have no conflict of interest.

Funding

We did not receive any of funding.

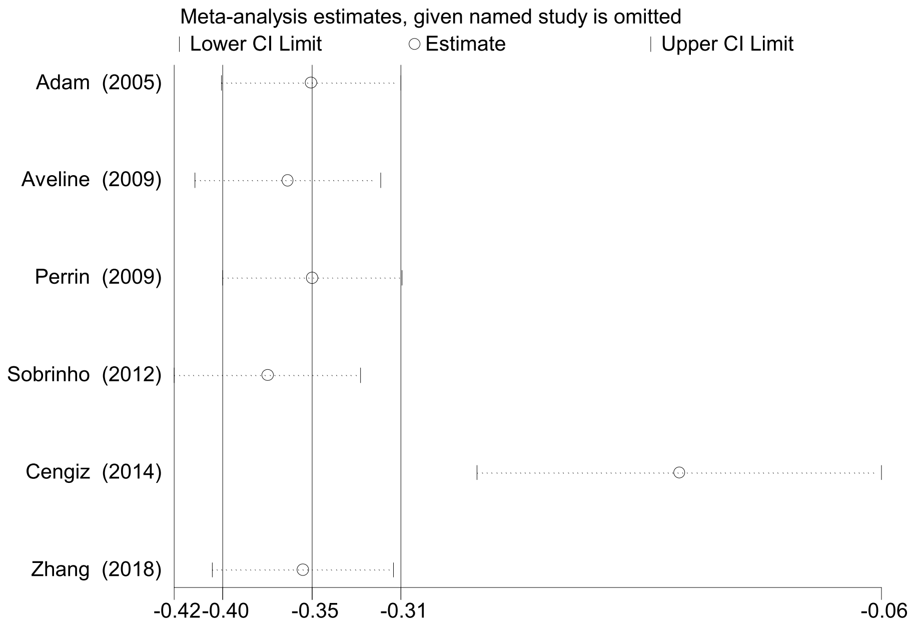


Fig. 10. Sensitivity analysis of pain score at 24 h.

Ethical approval

Ethical Approval was not required.

Research Registration Unique Identifying Number (UIN)

Unique Identifying Number (UIN): reviewregistry671.

https://www.researchregistry.com/browse-the-registry#registryofsystematicreviewsmeta-analyses/registryofsystematicreviewsmeta-analysesdetails/5c768ecf28acc558d79f7be0/

ISRCTN

This is a meta-analysis.

Author contribution

Zhenzhou Li: study design, data collections, data analysis, writing.
Yaru Chen: writing and language editing.

Guarantor

Zhenzhou Li and Yaru Chen.

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