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Analgesic effect of perioperative ketamine for total hip arthroplasties and total knee arthroplasties

A PRISMA-compliant meta-analysis

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Abstract

Background: Total hip arthroplasties (THA) and total knee arthroplasties (TKA) are always associated with a frequent incidence of postoperative pain. Effective pain management after surgery is quite essential for surgeons and patients. The purpose of the present meta-analysis is to evaluate the analgesic effect of perioperative ketamine after THA and TKA.

Methods: Seven online databases, Embase, Cochrane Library, Pubmed, Web of Science, China National Knowledge Infrastructure (CNKI), China Biomedical Literature Database (CBM), and Wanfang Data were searched for the related randomized controlled trials (RCT) by August 15, 2019. The qualities of the included studies were assessed based on the *Cochrane Handbook for Systematic Reviews of Interventions 5.0*. The visual analog scale (VAS), morphine equivalent consumption, and the side effects were used to evaluate the postoperative analgesic effect of ketamine by meta-analysis, which was performed by Review Manager version 5.3 software.

Results: The VAS scores at 6 hours, 12 hours, 24 hours, and 48 hours after surgery were statistically lower in the ketamine group. The morphine equivalent consumptions in 24 hours and 48 hours after surgery were also significantly lower in the ketamine group. For the side effects, no statistical differences in odds ratio (OR) of sedation, dizziness, hallucination, sweating, pruritus, urinary retention, constipation, version trouble, nightmares, and delirium were observed between the ketamine group and the control group. But postoperative nausea and vomiting (PONV) showed lower OR in the ketamine group.

Conclusion: The present meta-analysis demonstrated perioperative ketamine could be used as a safe and effective analgesic agent for THA and TKA.

Abbreviations: CBM = China Biomedical Literature Database, CI = confidence interval, CNKI = China National Knowledge Infrastructure, COX = cyclooxygenase, NMDA = N-methyl D-aspartate, NSAIDs = nonsteroidal anti-inflammatory drugs, OR = odds ratio, PCIA = patient-controlled intravenous analgesia, PONV = postoperative nausea and vomiting, RCT = randomized controlled trials, THA = total hip arthroplasties, TKA = total knee arthroplasties, VAS = visual analog scale, WMD = weighted mean difference.

Keywords: analgesia, ketamine, meta-analysis, total hip arthroplasties, total knee arthroplasties

1. Introduction

Given the aging society and the obesity epidemic, total hip and knee arthroplasties (THA/TKA), as highly effective surgery procedures, have been widely performed since 1970s.[1,2] In the United States, more than 700 thousand TKAs and 330 thousand THAs have been performed.[3] The number of THA and TKA performed in the US has been steadily increasing and is expected to exceed 4 million by 2030.[4] Both THA and TKA are painful processes, and effective pain management after surgery is critical to the evaluation of the outcome of the procedure.[5] Effective

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pain management has been shown to improve outcomes, including faster recovery, lower complication rates, lower care costs, and higher patient satisfaction.[6–8] Therefore, perioperative analgesia is extremely important for THA and TKA. Several analgesia protocols have been used in THA and TKA, including traditional oral opioids, femoral nerve block, intra-articular injection, and epidural analgesia.[9–11] However, each analgesic option has some limitations.[3] Currently, multimodal analgesia is demonstrated by many studies to be effective for pain control after THA and TKA.[3,5,7] The multimodal analgesia addresses multiple pain mechanisms and improves postoperative pain by combining pharmacologic and other modalities while reducing adverse effects using lower doses of individual modalities.[12–14] There is no immutable and standard protocol for multimodal analgesia. Multiple pathways and mediators are involved in nociception, and targeting several mechanisms can increase analgesic efficacy, using combinations of systemic and regional anesthesia. Various medications have been used in multimodal therapy, including nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase (COX)-2 inhibitors, acetaminophen, or paracetamol, neuromodulatory medications (gabapentin and pregabalin), opioid agonists, steroids, and N-methyl D-aspartate (NMDA) antagonists.[14]

Ketamine is a non-specific competitive NMDA receptor antagonist that produces anesthetic effects in large doses and anti-allergic, anti-allodynic, and opioid tolerance in small doses.[15] Because ketamine is highly lipid soluble, it allows for very rapid onset of its effect and is useful in general induction of anesthesia along with perioperative pain management.[16] The addition of ketamine in the multimodal analgesia regimen has been applied to many analgesic studies after THA and TKA. Many studies have been conducted to investigate ketamine as a modality in the multimodal approach to perioperative pain control and demonstrated that ketamine can provide superior pain relief, and reduced opioid dependence and opioid-related side effects, improving patient satisfaction, safety, and timely return to function.[17–19] However, no previous study meta-analyzed the analgesic effect of perioperative ketamine for total hip and knee arthroplasties. So, the purpose of the present meta-analysis is to evaluate the analgesic effect of perioperative ketamine after THA and TKA.

2. Material and methods

2.1. Literature searching strategy

Two independent investigators (Wang and Yang) thoroughly searched seven online databases, Embase, Cochrane Library, PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), China Biomedical Literature Database (CBM), and Wanfang Data by August 15, 2019. A combination of medical subject headings (MeSH) word and its corresponding entry word were utilized in the searching strategy. For example, the following refined PubMed/MeSH search words were: ((“Arthroplasty, Replacement, Hip” [MeSH Terms] OR “Arthroplasty, Replacement, Knee” [Mesh Terms]) AND (“Ketamine” [MeSH Terms]) AND “Analgesia” [MeSH Terms] AND “Randomized controlled trial” [Publication Type]); Then, the unrelated or improper studies were excluded by scanning abstracts, and the data was extracted from included studies by reading full texts carefully.

2.2. Inclusion and exclusion criteria

Studies with all of the following criteria were included into the systematic review and meta-analysis:

(1) randomized controlled trial and categorical sample contents;
(2) study on the analgesic effect of ketamine in THA or TKA;
(3) Visual analog scale (VAS), morphine equivalent consumption, or the side effects was used to evaluate the postoperative analgesia;
(4) sufficient data was provided to get weighted mean difference (WMD) and the corresponding 95% confidence interval (CI) or p values for diagnosis outcomes.

Studies were excluded with any of the following:

(1) repeated published data or studies;
(2) non-controlled studies;
(3) poor-quality or illogical statistically studies;
(4) not involved in the analgesic effect of ketamine in THA or TKA;
(5) provided data was not enough to get WMD or 95% CIs.

2.3. Data extraction and assessment of methodological quality

Literature screening, data extraction, and quality assessment were conducted according to inclusion and exclusion criteria by 2 independent investigators. The first author name, published year, surgery process, sample size, age, intervention mode, the anesthesia mode, and outcome data were extracted. VAS and morphine equivalent consumption were regarded as the primary outcome, and the side effect was considered to be the secondary outcome. The qualities of the included studies were assessed based on the *Cochrane Handbook for Systematic Reviews of Interventions 5.0* by 2 independent investigators (Wang and Yang). A table of “Risk of Bias” was conducted with the following parameters: random sequence generation, allocation concealment, blinding, incomplete outcome data, free of selective reporting, and other bias. Each parameter was recorded by “Yes”, “No”, and “Unclear”. A third investigator was needed with the occurrence of discrepancy after cross-checking. Each risk of bias item was presented as a percentage, which indicated the proportion of different levels of each risk of bias item, across all the included studies.

2.4. Statistical analysis

Meta-analysis was performed by Review Manager version 5.3 software, and the result was carried out by WMD due to the different units and 95% CI among the included literature. Cochran’s Q test and Higgens I^2 were used to evaluating the heterogeneity of the articles. If $P < .05$ and/or $I^2 > 50\%$, which represented the heterogeneity were significant, the random-effect module would be used; if not, the fixed-effect module would be used.

3. Results

3.1. Included studies

A total of 266 literature were collected independently by two investigators (Wang and Yang) in seven online databases after comprehensively searching based on the searching strategy: 10 in

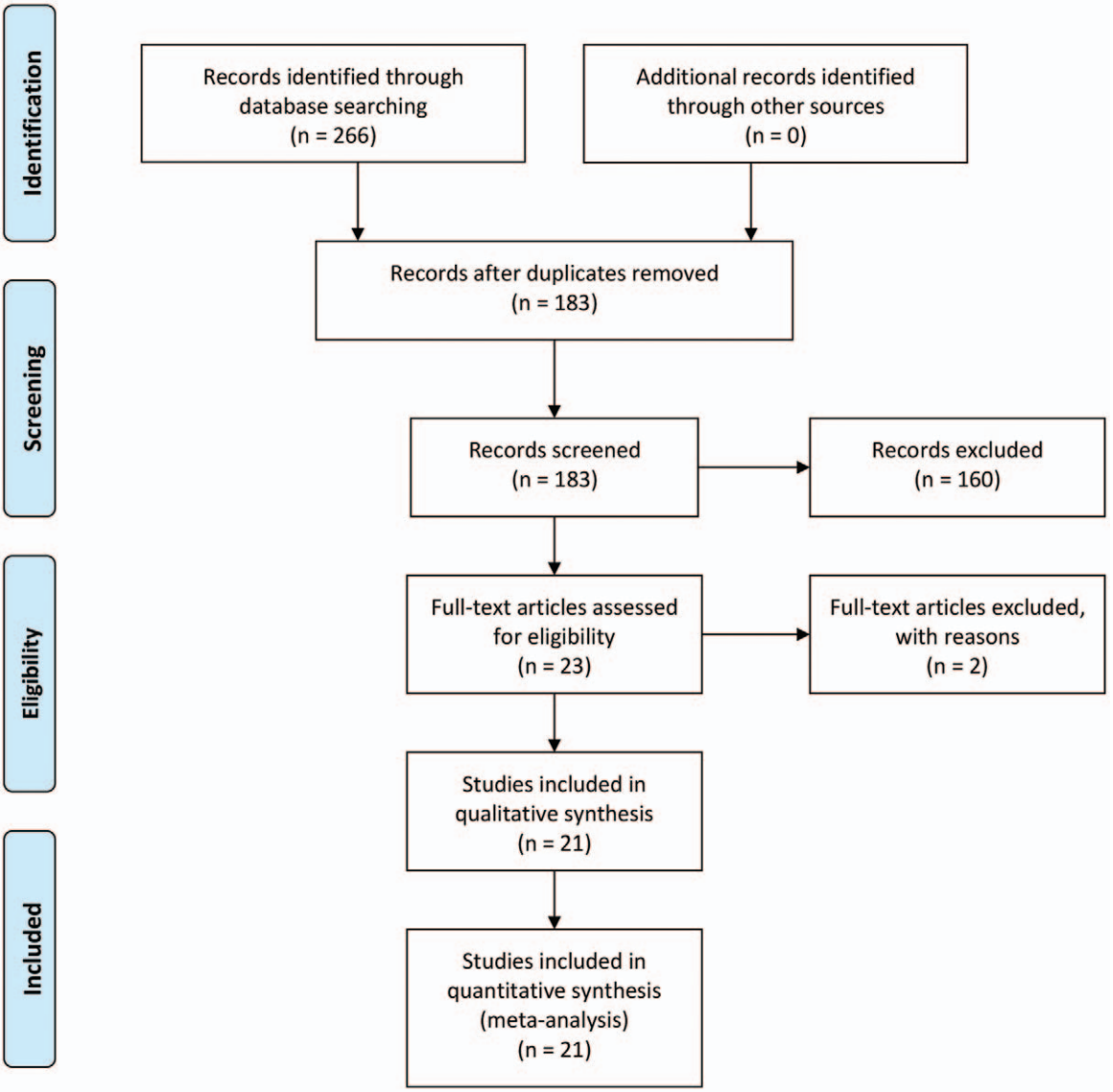

Figure 1. The flow diagram of literature search process.

PubMed, 34 in Embase, 31 in Cochrane Library, 105 in Web of Science, 36 in Wanfang Data, 31 in CBM, 19 in CNKI. A final decision was determined by a third independent investigator (Cao) when different opinions appeared. Of all the articles, 83 were excluded due to duplication, and another 160 were excluded on account of insufficient data, data duplication, and no full text. Finally, two records were removed because of repeatedly published data. In general, 21 studies were included in the present meta-analysis, the literature search process is shown in Figure 1.

3.2. Characteristics of the included studies

The sample size ranged from 12 to 154, and totally 1145 patients were included in the present meta-analysis. Patients in the experimental groups received ketamine treatment. The intravenous injection was performed in 10 of the included studies.[20–29] The intra-articular injection was performed in 2 of the included studies.[30,31] The epidural puncture injection was performed in 5 of the included studies.[32–36] Patient-controlled intravenous analgesia (PCIA) was performed in the other 4 studies.[21,37–39] Patients in the control groups received the placebo or normal saline with the same mode of corresponding experimental groups. All the included studies showed statistically similar baseline characteristics, which are showed in Table 1.

3.3. Risk of bias

We assessed the risk of bias of all the RCTs according to the *Cochrane Handbook for Systematic Review of Interventions*. Of all the included articles, one study (4.76%) did not report its randomization methodology which was considered as a high risk of bias. Twelve studies (57.14%) described their utilization of computer-generated randomization. Twelve studies (57.14%) reported their allocation concealment by using a closed envelope or label. Sixteen studies (76.19%) reported double blinding in the RCTs, and the blind investigators were also showed in outcome assessment. Eight studies (38.10%) did not report their

Table 1

Characteristics of the included studies.

Studies	Surgical procedure	Patient numbers (Female)		Age	Intervention
		Ketamine	Control		
Himmelseher, 2001[32]	TKA	18 (12)	19 (13)	65 ± 13	Patients in ketamine group received 0.25 mg/kg epidural ketamine 10 min before surgical incision.
Lauretti, 2005[33]	TKA	14 (6)	13 (5)	48 ± 17	Patients in ketamine group received 0.1 mg/kg epidural ketamine preoperatively.
Adam, 2005[20]	TKA	20 (14)	20 (13)	69 ± 7	Patients in ketamine group received an initial bolus of 0.5 mg/kg ketamine intravenously followed by a continuous infusion of 3 ug/kg/min during surgery and 1.5 ug/kg/min for 48 h after surgery.
Ma, 2005[34]	TKA	15 (7)	15 (9)	46 ± 14.9	Patients in ketamine group received 0.5 mg/kg epidural ketamine preoperatively.
Wang, 2007[21]	TKA	20 (14)	20 (13)	20–75	Patients in ketamine group received an initial bolus of 0.05 mg/kg ketamine intravenously followed by a continuous infusion of 3 ug/kg/min during surgery and 1.5 ug/kg/min for 48 h after surgery.
Liu, 2008[35]	THA	10 (4)	10 (5)	68.6 ± 10.49	Patients in ketamine group received 0.6 mg/kg epidural ketamine preoperatively.
Perrin, 2009[24]	TKA	5 (2)	7 (3)	62.5 ± 11.1	0.5 mg/kg of bolus intravenous ketamine was injected preoperatively followed by 4 μg/kg/min infusion during the surgery.
Remérand, 2009[25]	THA	79 (42)	75 (34)	64.5 ± 13.5	Patients in ketamine group received an initial bolus of 0.5 mg/kg ketamine intravenously followed by a continuous infusion of 2 ug/kg/min for 48 h after surgery.
Cagla Ozbakis Akkurt, 2009[23]	TKA	20 (9)	20 (10)	16–65	Patients in ketamine group received 0.15 mg/kg intravenous ketamine preoperatively.
Aveline, 2009[22]	TKA	25 (15)	24 (15)	71 ± 8	Patients in ketamine group received an initial bolus of 0.2 mg/kg ketamine intravenously followed by a continuous infusion of 120 ug/kg/h during surgery and 60 ug/kg/h for 48 h after surgery.
Zhai, 2010[36]	THA	30 (8)	30 (11)	70.5 ± 11.9	Patients in ketamine group received 30 mg epidural ketamine preoperatively.
Wang, 2011[40]	THA	60 (32)	30 (13)	76.6 ± 5.8	1mg/ml or 2mg/ml ketamine was injected postoperatively by patient-controlled intravenous analgesia with a bolus dose of 0.5 ml and a 15-min lockout.
Guará Sobrinho, 2012[30]	TKA	19 (16)	20 (17)		Patients in ketamine group received 0.25 mg/kg intra-articular ketamine postoperatively.
Zhao, 2012[26]	TKA	20 (14)	20 (12)	63.13 ± 8.62	Patients in ketamine group received an initial bolus of 1 mg/kg ketamine 10 min intravenously before surgery followed by a continuous infusion of 1mg/kg/h during surgery.
Chen, 2013[37]	TKA	30	30	70.9 ± 4.0	0.4 mg/ml ketamine was injected postoperatively by patient-controlled intravenous analgesia with a bolus dose of 2 ml and a 6-min lockout.
Martinez, 2014[28]	THA	34 (23)	38 (13)	18–80	Patients in ketamine group received intravenous ketamine with 0.5mg/kg bolus at the time of anesthesia induction immediately followed by 3ug/kg/h infusion stopped at skin closure.
Cengiz, 2014[27]	TKA	30 (25)	30 (19)	18–65	Patients in ketamine group received intravenous 6ug/kg/min ketamine during the surgery until would closure.
Ji, 2015[39]	TKA	25 (17)	25 (14)	50–70	2 mg/kg ketamine was injected postoperatively by patient-controlled intravenous analgesia with a bolus dose of 0.5 ml and a 15-min lockout.
Liu, 2015[38]	TKA	60 (50)	30 (26)	66.7 ± 5.5	1 mg/ml ketamine was injected postoperatively by patient-controlled intravenous analgesia with a bolus dose of 2 ml and a 60-min lockout.
Zhang, 2018[31]	TKA	21 (15)	23 (16)	42–74	Patients in ketamine group received 2 mg/kg intra-articular ketamine postoperatively.
Tan, 2019[29]	TKA	48 (28)	43 (25)	18-85	Patients in ketamine group received 60 mg intravenous ketamine at a rate of 6mcg/kg/min once situated on the table and was discontinued at skin closure.

incomplete outcome data. Low risk of bias of all the included studies due to selective outcome reporting was detected. The methodological quality assessment and the percentage of the risk of bias were shown in Figure 2 and Figure 3.

3.4. Meta-analysis of outcomes

3.4.1. Pain scores. Five studies, including 259 patients, reported VAS at 6 hours after surgery. Meta-analysis was performed through a fixed-effect model due to the insignificant heterogeneity ($I^2 = 42\%$, $P = .14$). The pooled results revealed that the VAS at 6 hours was statistically lower in the ketamine group than that in the control group (WMD = −1.45, 95% CI: −1.71 to −1.18, $P < .00001$; Fig. 4A).

Six studies, including 299 patients, reported VAS at 12 hours after surgery. Meta-analysis was performed through a random-effect model due to the significant heterogeneity ($I^2 = 91\%$, $P < .00001$). The pooled results revealed that the VAS at 12 hours was statistically lower in the ketamine group than that in the control group (WMD = −1.55, 95% CI: −2.28 to −0.82, $P < .0001$; Fig. 4B).

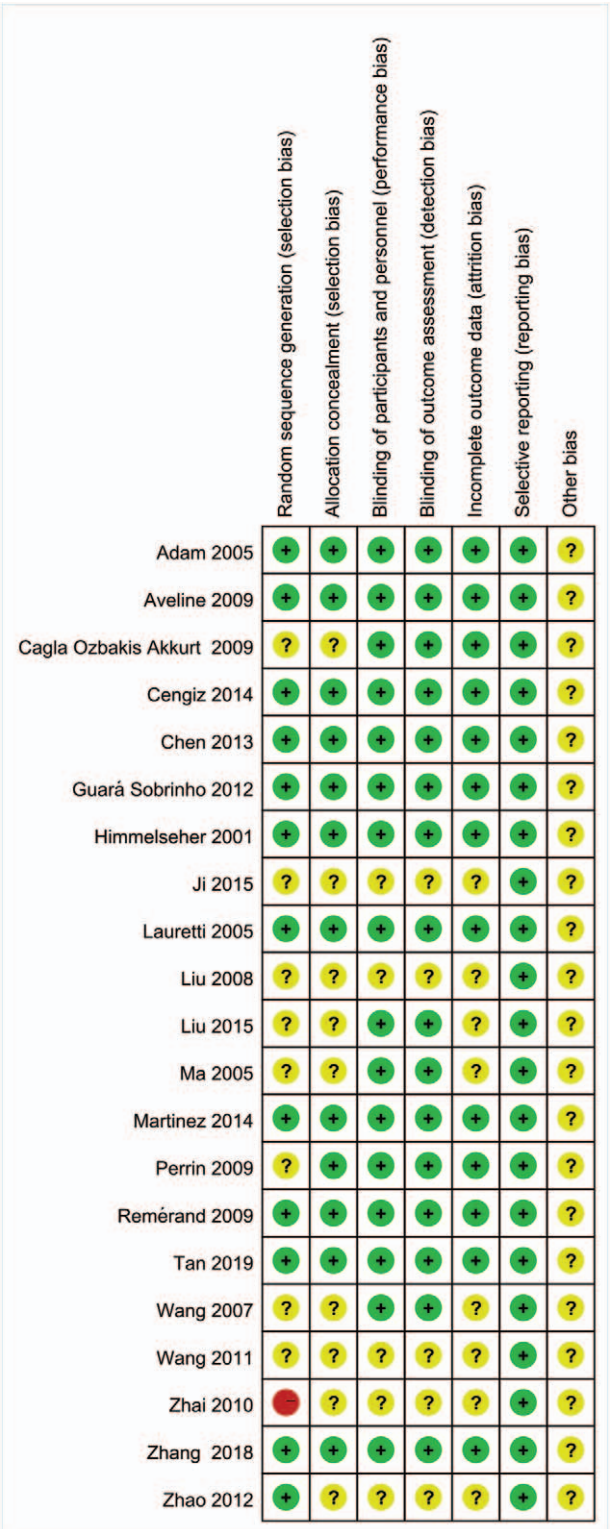

Figure 2. Assessment of methodological quality of the included studies.

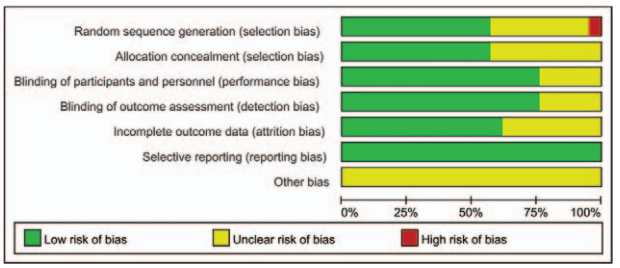

Figure 3. The percentage summary of risk of bias.

Thirteen studies, including 732 patients, reported VAS at 24 hours after surgery. Meta-analysis was performed through a random-effect model due to the significant heterogeneity (I^2 = 90%, P < .00001). The pooled results revealed that the VAS at 24 hours was statistically lower in the ketamine group than that in the control group (WMD = −0.78, 95% CI: −1.25 to −0.31, P = .001; Fig. 4C).

Seven studies, including 534 patients, reported VAS at 48 hours after surgery. Meta-analysis was performed through a random-effect model due to the significant heterogeneity (I^2 = 92%, P < .00001). The pooled results revealed that the VAS at 48 hours was statistically lower in the ketamine group than that in the control group (WMD = −0.74, 95% CI: −1.26 to −0.22, P = .006; Fig. 4D).

3.4.2. Morphine equivalent consumption. The morphine equivalent consumptions at 24 hours after surgery were reported in five studies, including 315 patients. Meta-analysis was performed through a random-effect model due to the significant heterogeneity (I^2 = 96%, P < .00001). The pooled results revealed that the morphine equivalent consumption at 24 hours was significantly lower in the ketamine group than that in the control group (WMD = −17.58, 95% CI: −29.07 to −6.10, P = .003; Fig. 5A).

The morphine equivalent consumptions at 48 hours after surgery were reported in 5 studies, including 299 patients. Meta-analysis was performed through a random-effect model due to the significant heterogeneity (I^2 = 94%, P < .00001). The pooled results revealed that the morphine equivalent consumption at 48 hours was significantly lower in the ketamine group than that in the control group (WMD = −16.82, 95% CI: −27.75 to −5.89, P = .003; Fig. 5B).

3.4.3. Side effects. The meta-analysis of the odds ratio (OR) for sedation, dizziness, hallucination, PONV, sweating, pruritus, urinary retention, constipation, version trouble, nightmares, delirium were performed. Because different studies reported different side effects, the meta-analysis of each side effect included various amounts of studies.

Thirteen studies, including 721 patients, reported PONV after surgery. Meta-analysis was performed through a fixed-effect model due to the insignificant heterogeneity (I^2 = 0%, P = .48). Statistically lower OR was observed in the ketamine group than that in the control group after the pooled analysis (OR = 0.54, 95% CI: 0.37 to 0.77, P = .0008). The meta-analysis of the other side effects showed no differences between the two groups. The details are shown in Table 2.

4. Discussion

The present meta-analysis evaluated the analgesic effect of perioperative ketamine after THA and TKA. The VAS scores at 6 hours, 12 hours, 24 hours, and 48 hours after surgery were statistically lower in the ketamine group than those in the control group. The morphine equivalent consumptions in 24 hours and

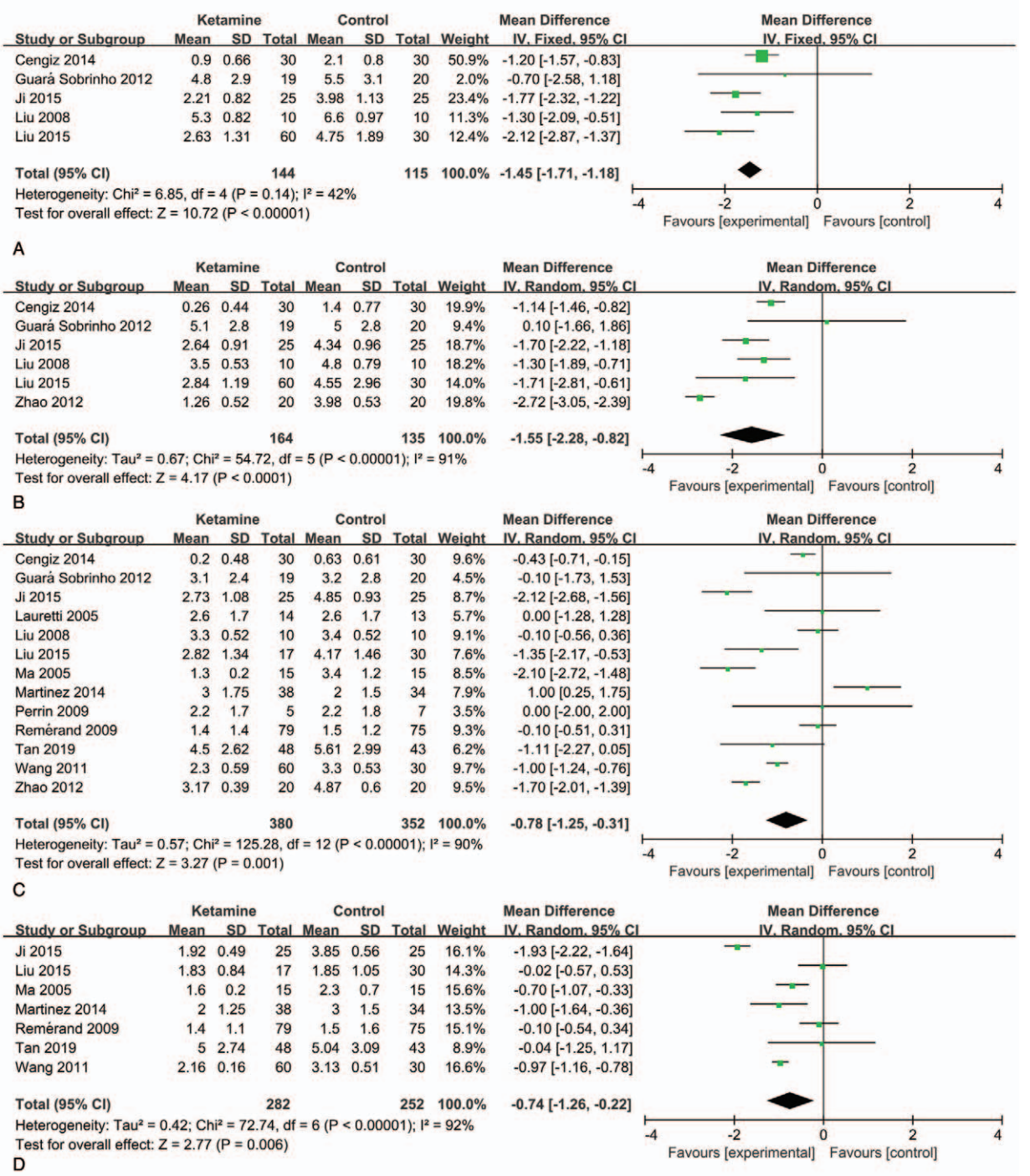

Figure 4. Forest plot of visual analog scale (VAS) scores in the ketamine group and the control group after surgery. A, VAS scores at 6 hours after surgery; B, VAS scores at 12 hours after surgery; C, VAS scores at 24 hours after surgery; D, VAS scores at 48 hours after surgery.

48 hours after surgery were also significantly lower in the ketamine group. For the side effects, no statistical differences in OR of sedation, dizziness, hallucination, sweating, pruritus, urinary retention, constipation, version trouble, nightmares, and delirium were observed between the ketamine group and the control group. But PONV showed lower OR in the ketamine group. THA and TKA are always associated with a frequent incidence of postoperative pain.[32,41] Uncontrolled pain increases the risk of complications, morbidity, and some other adverse effects such as sleep disorder and anxiety, thereby hindering physical therapy, rehabilitation, and increasing length of hospital stay.[41] Wall first proposed the term multimodal pain management in 1988.[42] In recent years, various analgesic patterns have been suggested for minimizing the pain after arthroplasty, including the utilization of ketamine, which has been discussed in a large number of studies as supplemental analgesia for perioperative pain control.[43,44] However, whether the analgesic effect of ketamine for THA and TKA holds true is

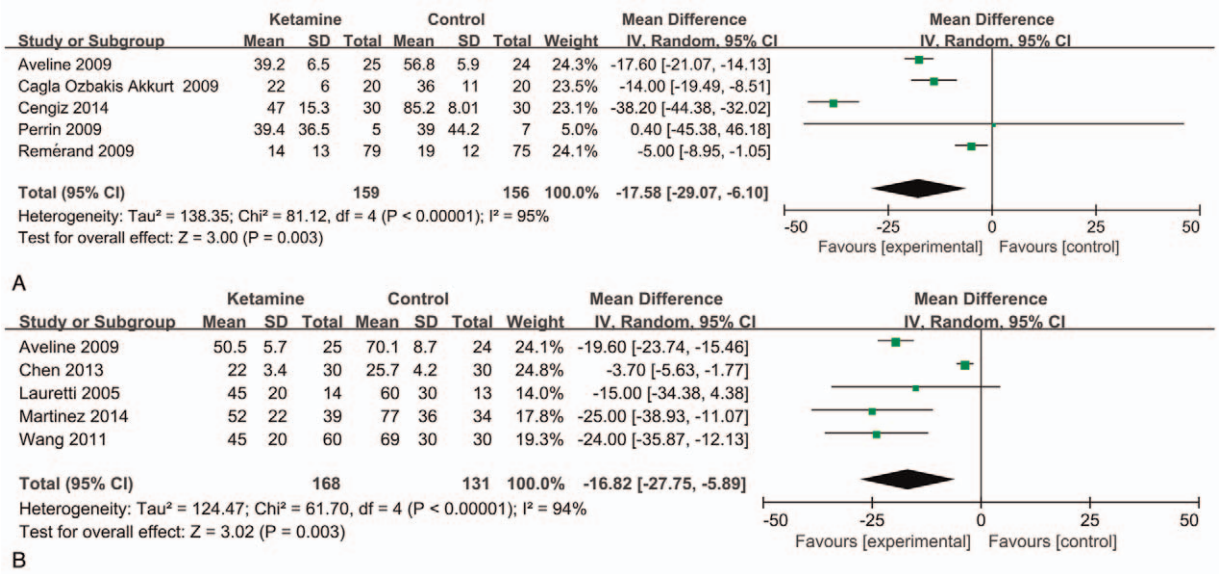

Figure 5. Forest plot of morphine equivalent consumption in the ketamine group and the control group after surgery. A, morphine equivalent consumption at 24 hours after surgery; B, morphine equivalent consumption at 48 hours after surgery.

still a question. To the best of our knowledge, this is the first meta-analysis to investigate the analgesia effect of perioperative and postoperative ketamine for THA and TKA. Our results confirmed that the perioperative application of ketamine could reduce postoperative pain in patients.

Ketamine, a classical antagonist of NMDA excitatory glutamate receptor, mainly exerts analgesia by selectively acting on the brain contact pathway and the new cortical system of the thalamus. It plays the biological roles by inhibiting the transmission of the spinal cord to the reticular structure to the central nervous system, exciting the medulla and marginal system, and inhibiting the non-specific nuclei of the midbrain and thalamus.[45–48] Therefore, ketamine has been increasingly used in a range of diseases as well as treatment-induced pain.[43]

VAS score and morphine equivalent consumption are always used as regular and objective indicators to evaluate the postoperative pain control in most of the analgesia studies, and they are considered as the primary outcome to evaluate the postoperative pain in the present meta-analysis. We meta-analyzed VAS scores at 6 hours, 12 hours, 24 hours, and 48 hours after surgery. The pooled results in all the comparison groups showed statistically lower scores in the ketamine groups than that in the control groups. The morphine equivalent consumption was also meta-analyzed in 24 hours and 48 hours after surgery. The pooled results in both groups revealed significantly less morphine equivalent consumption in the ketamine groups than those in the control groups. All the evidence demonstrated perioperative ketamine could be used as a supplementary analgesic agent in multimodal pain management strategy. Interestingly, as the time after surgery increased, the WMD of the VAS scores and morphine equivalent consumption at each time point gradually decreased. The decreasing trend may be related to the short half-life of ketamine and indicated that the analgesic effect of ketamine might be more effective in the early postoperative period.[29]

In addition, although the present meta-analysis showed the lower VAS scores and the less morphine equivalent consumption of patients in the ketamine groups, we have to note that ketamine is an addictive drug that may cause psychedelic experiences such as delusions, hallucinations, confusion, cognitive dysfunction, delirium, and mystical experiences.[49–51] The psychological effect is related to the dose of ketamine.[49,52] However, a large number of clinical studies have shown that the subanesthetic dose

Table 2

Meta-analysis result of the side effects.

Side Effect	Included studies	Included patients	Odds Ratio (OR) [95% CI]	*P*	I^2	*P* value of Heterogeneity
Sedation	2 [28, 31]	111	0.94 [0.29, 3.09]	.92	0%	.39
Dizziness	7 [26, 28, 30, 31, 35, 36, 39]	321	1.15 [0.43, 3.06]	.79	0%	.59
Hallucination	5 [25–28, 30]	365	0.73 [0.30, 1.78]	.49	0%	.95
PONV	13 [20, 22, 25–28, 30–32, 35–37, 39]	721	0.54 [0.37, 0.77]	.0008	0%	.48
Sweating	2 [22, 31]	89	1.15 [0.15, 8.53]	.89	0%	.86
Pruritus	5 [25, 26, 28, 35, 37]	346	1.20 [0.57, 2.50]	.63	0%	.55
Urinary retention	6 [22, 25, 28, 31, 32, 35]	372	1.12 [0.58, 2.16]	.73	0%	.94
Constipation	2 [28, 31]	129	1.29 [0.41, 4.03]	.71	73%	.06
Version trouble	4 [25–27, 35]	274	1.13 [0.34, 3.69]	.84	44%	.17
Nightmares	2 [25, 30]	193	1.19 [0.54, 2.64]	.66	0%	.53
Delirium	2 [30, 37]	29	5.86 [0.26, 130.26]	-	-	.26

of ketamine has a central nervous analgesic effect with minimal impact on consciousness and cognition. None of the included study reported the side effect of post-operative cognitive dysfunction. It was demonstrated infrequent or recreational ketamine use does not appear to be associated with long-term cognitive impairment.[50] Therefore, it can be used as a safe analgesic agent, especially for acute pain in the perioperative period, which is currently determined by the World Health Organization as a crucial drug for the administration of many other anesthetics.[19,49,50,53] Further, the toxicity of ketamine can cause a variety of neurological, cardiovascular, psychiatric, genitourinary, and abdominal symptoms, which are dose-dependent.[54,55] In the present study, we meta-analyzed the side effects of the included study. The ketamine group showed a lower pooled OR of PONV than the control group. The meta-analysis of the other side effects showed no differences between the 2 groups, which might be due to the small dose of ketamine applied in most included studies. Our results further confirmed the safety of small-dose ketamine for analgesia.

There are some limitations to the present meta-analysis. First, due to the different doses of ketamine used in each included study, we did not investigate the impact of the dose of ketamine. At present, there is no research report on the most suitable ketamine dose for perioperative evaluation of efficacy and safety.[43] In addition, different anesthesia methods may affect postoperative pain control.[41] These might be the cause of high heterogeneity. Second, only short-term outcomes (<48 hours) were investigated in the present study. Therefore, further studies about the analgesic effect of ketamine are still required in the future to determine the ideal patients and conditions for ketamine treatment and the ideal dose for analgesia.[56]

5. Conclusion

The present study meta-analyzed the analgesia effect of perioperative ketamine for THA and TKA. The statistically lower VAS scores at 6 hours, 12 hours, 24 hours, and 48 hours after surgery and lower morphine equivalent consumptions in 24 hours and 48 hours after surgery were observed. These findings demonstrated the analgesic effect of perioperative ketamine for THA and TKA. The analysis of side effects further confirmed the safety of ketamine for analgesia. All the evidence indicated that perioperative ketamine could be used as a safe and effective analgesic agent for THA and TKA.

Author contributions

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Funding Acquisition: Zhipeng Cao
Methodology: Peng Wang, Zhong Yang, Shimin Shan
Software: Zhilin Wang
Supervision: Zhipeng Cao, Zhilin Wang
Validation: Zhipeng Cao, Zhilin Wang
Writing – original draft: Peng Wang, Zhong Yang
Writing – review & editing: Zhipeng Cao, Zhilin Wang

References

[1] Gademan MG, Hofstede SN, Vliet Vlieland TP, et al. Indication criteria for total hip or knee arthroplasty in osteoarthritis: a state-of-the-science overview. BMC Musculoskelet Disord 2016;17:463.
[2] Memtsoudis SG, Pumberger M, Ma Y, et al. Epidemiology and risk factors for perioperative mortality after total hip and knee arthroplasty. J Orthop Res 2012;30:1811–21.
[3] Yang L, Du S, Sun Y. Intravenous acetaminophen as an adjunct to multimodal analgesia after total knee and hip arthroplasty: a systematic review and meta-analysis. Int J SurgV 47 2017;135–46.
[4] Memtsoudis SG, Sun X, Chiu YL, et al. Utilization of critical care services among patients undergoing total hip and knee arthroplasty: epidemiology and risk factors. Anesthesiology 2012;117:107–16.
[5] Hannon CP, Keating TC, Lange JK, et al. Anesthesia and analgesia practices in total joint arthroplasty: a survey of the american association of hip and knee surgeons membership. J Arthroplasty 2019;34:2872–7.
[6] Tali M, Maaroos J. Lower limbs function and pain relationships after unilateral total knee arthroplasty. Int J Rehabil Res 2010;33:264–7.
[7] Lamplot JD, Wagner ER, Manning DW. Multimodal pain management in total knee arthroplasty: a prospective randomized controlled trial. J Arthroplasty 2014;29:329–34.
[8] Parvizi J, Porat M, Gandhi K, et al. Postoperative pain management techniques in hip and knee arthroplasty. Instr Course Lect 2009;58: 769–79.
[9] Wang X, Sun Y, Wang L, et al. Femoral nerve block versus fascia iliaca block for pain control in total knee and hip arthroplasty: a meta-analysis from randomized controlled trials. Medicine (Baltimore) 2017;96:e7382.
[10] Jiang J, Teng Y, Fan Z, et al. The efficacy of periarticular multimodal drug injection for postoperative pain management in total knee or hip arthroplasty. J Arthroplasty 2013;28:1882–7.
[11] Lauretti GR, Righeti CC, Mattos AL. Intrathecal ketorolac enhances intrathecal morphine analgesia following total knee arthroplasty. J Anaesthesiol Clin Pharmacol 2013;29:503–8.
[12] Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. Am J Surg 2002;183:630–41.
[13] Ekman EF, Koman LA. Acute pain following musculoskeletal injuries and orthopaedic surgery: mechanisms and management. Instr Course Lect 2005;54:21–33.
[14] Kohring JM, Orgain NG. Multimodal analgesia in foot and ankle surgery. Orthop Clin North Am 2017;48:495–505.
[15] Carstensen M, Moller AM. Adding ketamine to morphine for intravenous patient-controlled analgesia for acute postoperative pain: a qualitative review of randomized trials. Br J Anaesth 2010;104:401–6.
[16] Helander EM, Menard BL, Harmon CM, et al. Multimodal analgesia, current concepts, and acute pain considerations. Curr Pain Headache Rep 2017;21:3.
[17] Laskowski K, Stirling A, McKay WP, et al. A systematic review of intravenous ketamine for postoperative analgesia. Can J Anaesth 2011;58:911–23.
[18] Jouguelet-Lacoste J, La Colla L, Schilling D, et al. The use of intravenous infusion or single dose of low-dose ketamine for postoperative analgesia: a review of the current literature. Pain Med (Malden, Mass) 2015;16:383–403.
[19] Gorlin AW, Rosenfeld DM, Ramakrishna H. Intravenous sub-anesthetic ketamine for perioperative analgesia. J Anaesthesiol Clin Pharmacol 2016;32:160–7.
[20] Adam F, Chauvin M, Du Manoir B, et al. Small-dose ketamine infusion improves postoperative analgesia and rehabilitation after total knee arthroplasty. Anesth Analg [Article] 2005;100:475–80.
[21] Wang F. Low-dose ketamine improves analgesia quality and rehabilitation after total knee arthroplasty. J North China Univ Sci Technol (Health Sciences Edition) 2007;9:779–81.
[22] Aveline C, Gautier JF, Vautier P, et al. Postoperative analgesia and early rehabilitation after total knee replacement: a comparison of continuous low-dose intravenous ketamine versus nefopam. Eur J Pain (London, England) 2009;13:613–9.
[23] Cagla Ozbakis Akkurt B, Inanoglu K, Kalaci A, et al. Effects of intravenous small dose ketamine and midazolam on postoperative pain following knee arthroscopy. Pain Pract [Article] 2009;9:289–95.
[24] Perrin SB, Purcell AN. Intraoperative ketamine may influence persistent pain following knee arthroplasty under combined general and spinal anaesthesia: a pilot study. Anaesth Intensive Care [Article] 2009;37: 248–53.
[25] Remerand F, Le Tendre C, Baud A, et al. The early and delayed analgesic effects of ketamine after total hip arthroplasty: a prospective, randomized, controlled, double-blind study. Anesth Analg 2009;109: 1963–71.
[26] Zhao T. Application of intravenous low-dose ketamine for preemptive analgesia in total knee arthroplasty. China Modern Med 2012;19:86–7.

[27] Cengiz P, Gokcinar D, Karabeyoglu I, et al. Intraoperative low-dose ketamine infusion reduces acute postoperative pain following total knee replacement surgery: a prospective, randomized double-blind placebo-controlled trial. J Coll Physicians Surg Pak V 24 2014;299–303.
[28] Martinez V, Cymerman A, Ben Ammar S, et al. The analgesic efficiency of combined pregabalin and ketamine for total hip arthroplasty: a randomised, double-blind, controlled study. Anaesthesia 2014;69:46–52.
[29] Tan TL, Longenecker AS, Rhee JH, et al. Intraoperative ketamine in total knee arthroplasty does not decrease pain and narcotic consumption: a prospective randomized controlled trial. J Arthroplasty 2019;34: 1640–5.
[30] Guara Sobrinho H, Garcia JB, Vasconcelos JW, et al. Analgesic efficacy of the intra-articular administration of S(+)- ketamine in patients undergoing total knee arthroplasty. Rev Bras Anestesiol 2012;62:665–75.
[31] Zhang J, Shi K, Jia H. Ketamine and bupivacaine attenuate post-operative pain following total knee arthroplasty: a randomized clinical trial. Exp Ther Med [Article] 2018;15:5537–43.
[32] Himmelseher S, Ziegler-Pithamitsis D, Argiriadou H, et al. Small-dose S (+)-ketamine reduces postoperative pain when applied with ropivacaine in epidural anesthesia for total knee arthroplasty. Anesth Analg 2001;92:1290–5.
[33] Lauretti GR, Rodrigues AM, Paccola CA, et al. The combination of epidural clonidine and S(+)-ketamine did not enhance analgesic efficacy beyond that for each individual drug in adult orthopedic surgery. J Clin Anesth 2005;17:79–84.
[34] Ma H, Wang G. The postoperative analgesic effects of epidural ketamine in patients undergoing total knee replacement surgery. Hebei Med J 2005;27:579–80.
[35] Liu D, Lv Z, Liu M. Epidural ketamine and clonidine in preemptive anagesia for total hip replacement. Pain Clin J 2008;2:35–9.
[36] Zhai Q. Comparison of the effects of low-dose ketamine and tramadol on hip replacement in elderly patients. Chin J Prim Med Pharm 2010; 17:1395–6.
[37] Chen J, Li J, Wang D. Effect of small dose ketamine combined with morphine used for postoperative analgesia in elderly patients undergoing total knee replacement surgery. Chin J Geriatr 2013;32:1322–5.
[38] Liu M, Liao R, Yu J, et al. The effect of small dose ketamine for postoperative analgesia after total knee arthroplasty under unilateral spinal anesthesia. J Guangdong Med Coll 2015;33:205–7.
[39] Ji S, Yao F, Huang L, et al. Outcomes of postoperative analgesia with ketamine combined with sufentanyl in patients after total knee replacement. Jiangsu Med J 2015;41:1786–8.
[40] Wang S, Li Y, Tan P, et al. Low-dose ketamine combined with sufentanil PCIA for postoperative analgesia after hip replacement. Chin Manip Rehab Med 2011;2:113.
[41] Gaffney CJ, Pelt CE, Gililland JM, et al. Perioperative pain management in hip and knee arthroplasty. Orthop Clin North Am 2017;48:407–19.
[42] Wall PD. The prevention of postoperative pain. Pain 1988;33:289–90.
[43] Bhatia A. Ketamine as an adjunct to patient-controlled analgesia: why, for whom, and how much? Can J Anaesth 2016;63:262–4.
[44] Pendi A, Field R, Farhan SD, et al. Perioperative ketamine for analgesia in spine surgery: a meta-analysis of randomized controlled trials. Spine (Phila Pa 1976) 2018;43:E299–307.
[45] Rogers R, Wise RG, Painter DJ, et al. An investigation to dissociate the analgesic and anesthetic properties of ketamine using functional magnetic resonance imaging. Anesthesiology 2004;100:292–301.
[46] Petrenko AB, Yamakura T, Baba H, et al. The role of N-methyl-D-aspartate (NMDA) receptors in pain: a review. Anesth Analg 2003; 97:1108–16.
[47] Niesters M, Martini C, Dahan A. Ketamine for chronic pain: risks and benefits. Br J Clin Pharmacol 2014;77:357–67.
[48] Khalili-Mahani N, Niesters M, van Osch MJ, et al. Ketamine interactions with biomarkers of stress: a randomized placebo-controlled repeated measures resting-state fMRI and PCASL pilot study in healthy men. Neuroimage 2015;108:396–409.
[49] Ivan Ezquerra-Romano I, Lawn W, Krupitsky E, et al. Ketamine for the treatment of addiction: evidence and potential mechanisms. Neuropharmacology 2018;142:72–82.
[50] Morgan CJ, Curran HV. Independent Scientific Committee on DKetamine use: a review. Addiction 2012;107:27–38.
[51] Zhu W, Ding Z, Zhang Y, et al. Risks associated with misuse of ketamine as a rapid-acting antidepressant. Neurosci Bull 2016;32:557–64.
[52] Jansen KL, Darracot-Cankovic R. The nonmedical use of ketamine, part two: a review of problem use and dependence. J Psychoactive Drugs 2001;33:151–8.
[53] Himmelseher S, Durieux ME. Ketamine for perioperative pain management. Anesthesiology 2005;102:211–20.
[54] Orhurhu VJ, Claus LE, Vashisht R, Cohen SP. Ketamine Toxicity. 2020 Jul 10. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan–. PMID: 31082131.
[55] Bokor G, Anderson PD. Ketamine: an update on its abuse. J Pharm Pract 2014;27:582–6.
[56] Orhurhu V, Orhurhu MS, Bhatia A, et al. Ketamine infusions for chronic pain: a systematic review and meta-analysis of randomized controlled trials. Anesth Analg 2019;129:241–54.