Meta-Analysis

Impact of Ketamine on Pain Management in Cesarean Section: A Systematic Review and Meta-Analysis

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Background: The pain control effect of ketamine versus control in women during cesarean operation is not well determined.

Objectives: The present meta-analysis aimed to evaluate the clinical efficacy of ketamine versus control in cesarean section anesthesia for reducing the postoperative pain and analgesia.

Study Design: We used meta-analysis to address this concern.

Setting: Meta-analysis-based study.

Methods: The databases PubMed, Embase, and the Cochrane Library were systematically searched to identify the relevant randomized controlled trials (RCTs) of ketamine versus control in controlling pain after cesarean section from inception to August 2018. Based on the Cochrane Handbook, the combined analysis was performed using Revman 5.3 software.

Results: A total of 20 RCTs with 1,737 patients who underwent cesarean section were included. Meta-analysis showed that the pain score in the ketamine group was less than that of the control group (mean difference [MD], –1.10; 95% confidence interval [CI], –1.61, –0.59; $P < 0.0001$). Application of ketamine during cesarean section also resulted in decreased consumption of morphine when compared with the control group (MD, –6.11 mg; 95% CI, –9.93, –2.29; $P = 0.002$). In addition, the first time required for analgesia was significantly longer in the ketamine group than that of the control group (MD, 72.48 minutes; 95% CI, 50.85, 94.11; $P < 0.00001$).

Limitations: Limited patients were included with moderate strength.

Conclusions: Ketamine supplementation during cesarean section reduces pain and morphine consumption and prolongs the postoperative analgesia.

Key words: Ketamine, cesarean section, randomized controlled trials, meta-analysis

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Tissue trauma causes central sensitization of the spinal dorsal horn neurons through N-methyl-D-aspartate (NMDA) receptor-related mechanisms, which in turn produces secondary hyperalgesia (1). Postoperative mechanical hyperalgesia occurs in both tissue trauma and the areas of inflammation (primary hyperalgesia), as well as noninvasive noninflammatory tissues (secondary hyperalgesia) in the adjacent areas (2). Primary hyperalgesia occurs primarily because of the sensitization of peripheral nociceptors, and the secondary mechanical hyperalgesia is because of the central sensitization of the spinal cord (3). Ketamine is a selective noncompetitive NMDA receptor antagonist (4). Also, it reduces pain by reducing the NMDA receptor-mediated secondary pain (5). Animal experiments showed that antagonizing the NMDA receptors can prevent central sensitization, reverse the central sensitization, and reduce the opioid tolerance (5,6).

A large number of clinical trials investigated the analgesic effects of ketamine, which is often used to treat the neuropathic pain or combined with opioids in the treatment of intractable pain in patients with cancer or other pain (7-9). Furthermore, ketamine infusions during and after surgery can effectively reduce the mechanical hyperalgesia around the surgical incision, which lasts up to 7 days postsurgery (10). In addition, ketamine is often used as an adjunct to postoperative analgesia. A meta-analysis (11) included a total of 37 clinical studies. The results indicated that the intraoperative subdose of ketamine reduces the amount of postoperative analgesic medication and/or postoperative pain intensity. Another meta-analysis (12) evaluated the efficacy of the drugs in preventing chronic pain postsurgery. A total of 14 randomized controlled trials (RCTs) on ketamine were included in the analysis, as only ketamine could moderately reduce the postoperative chronic pain (P = 0.001). Whether ketamine exhibits a similar role in pain management of cesarean section is not yet determined in these studies. The systematic review in 2015 by Heesen et al (13) evaluated the role of ketamine in pain management of cesarean section, as well as adverse events. A total of 12 RCTs were included. They found that ketamine could improve postoperative analgesia after caesarean section under spinal anesthesia. Here we tried to perform a up-to-date systematic review and meta-analysis to further evaluate the pain control effect of ketamine in patients who underwent cesarean section.

Thus in this study, we selected RCTs that used ketamine versus control during cesarean section and aimed to assess the clinical efficacy of ketamine in reducing postoperative pain and analgesia in cesarean section.

Methods

Search Sources and Strategies

Databases including PubMed, Embase, and the Cochrane Library were searched for RCTs comparing the clinical efficacy of ketamine versus other agents on pain management in patients who underwent cesarean section. The terms of "ketamine," "cesarean section," "abdominal delivery," "caesarean delivery," "parturient," "pain," "VAS," "NRS," "Visual Analog Scale," and "Numeric Rating Scale" were used in different combinations during the literature search from the establishment of the database up to August 2018. The recommended references by the databases were also reviewed to ensure complete screening during the search. Language restriction was not applied in this study.

Inclusion Criteria

Study type: clinical RCTs using ketamine versus control in pain management for patients who underwent cesarean section were included. Patients: those who underwent cesarean section and fulfilled the following criteria, such as American Society of Anesthesiologists grade I-II, elective full-term maternal, no major life events before birth, no severe pathological obstetrics, no severe complications such as hyperthyroidism, hypertension, and no history of mental illness, brain disease, drug abuse, or allergy. Interventions: in the experimental group, ketamine was administered intravenously or intraspinally for spinal anesthesia during cesarean section. Saline solution or other anesthetic agents were used as control similar to that of anesthesia. Outcomes: pain relief, the time point for the first request of analgesics, and morphine consumption.

Exclusion Criteria

Replications, reviews, animal experiments, studies with insufficient data, or high-risk bias were excluded.

Data Extraction

Two reviewers conducted the literature screening and data extraction based on the inclusion and exclusion criteria independently. In the case of disagreement, the study was reevaluated or submitted to the third evaluator for decision. The extracted data included the basic information of the included studies and patients, study type, intervention, and outcome measures.

Quality Assessment

The risk of bias was assessed according to the Cochrane Handbook (14) based on the 7 aspects: random assignment method, allocation scheme concealment, study blind method, outcome measure blindness, the integrity of the resulting, selective reporting, and other sources of bias. All aspects were evaluated based on "low bias," "unclear bias," and "high biased."

Statistical Analysis

Meta-analysis was performed using RevMan 5.3 software (The Nordic Cochrane Centre for The Cochrane Collaboration, Copenhagen, Denmark) (14). For the enumeration data, the odds ratio and the 95% confidence interval (CI) were used as the effect indicators. For the measurement data, the mean difference (MD) and related 95% CI were used as the effect indicators. The chi-square test was used to detect the heterogeneity of the included studies. If $P > 0.1$ and $I^2 < 50\%$, homogeneity occurred between the included studies

and the fixed effect model was used for meta-analysis. If significant heterogeneity was detected between the studies, the source of heterogeneity was analyzed, and the random-effects model was applied for the overall analysis. The significant level of the meta-analysis was set at $P < 0.05$, and the combined results were presented using a forest plot. Subgroup analyses were performed based on the analgesic drug types, pain evaluation method, and region.

Results

Search Results and Baseline Characteristics of Included Studies

A total of 217 studies were screened, and of these 43 were excluded due to irrelevant or duplicate literature. After reviewing the title and abstract of 174 articles, 23 articles were included. After reading the full text, 20 RCTs (15-34) were finally included as eligible studies for the meta-analysis. All the studies were published in the English language. Three out of 20 studies reported the efficacy of ketamine in decreasing pain score, 4 out of 20 studies reported the time of the first request for postoperative anesthesia, and 3 out of 20 studies reported the consumption of morphine. Six studies used general analgesia and the rest used spinal analgesia during operation. The specific screening process is illustrated in Fig. 1. The basic characteristics of the included studies are shown in Table 1.

Quality Assessment

The overall quality of the included studies was high as they were RCTs applied with blinding. The summary and details of quality assessment are presented in Figs. 2 and 3.

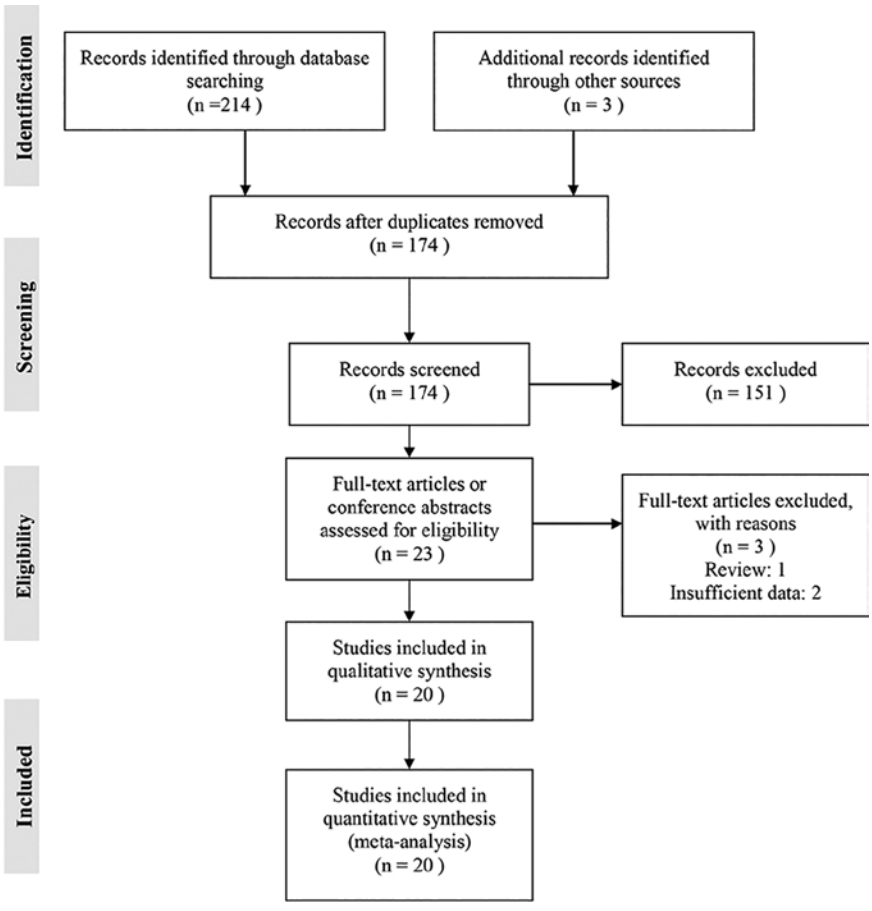

Fig. 1. *The overall process of study selection and identification.*

Table 1. *Baseline characteristics of included studies*

Author	Year	Design	Number in T	Number in C	Region	Age		Patient type	Treatment	Control	Outcomes
						Ketamine	Control				
Basuni AS	2016	RCT	25	25	Africa	29.7 ± 3.8	28.5 ± 4.5	Cesarean section	Ketamine (10 mg), midazolam (2 mg), and 0.5% hyperbaric bupivacaine (8 mg) in group ketamine-midazolam-bupivacaine (KMB)	Fentanyl (25 μg) and 0.5% hyperbaric bupivacaine (8 mg) in group fentanyl-bupivacaine (FB)	Heart rate (HR), mean arterial blood pressure, oxygen saturation, sensorimotor block characteristics, pain-free period, side effects, and patients' satisfaction VAS.
Bauchat J	2011	RCT	94	94	America	34 [31-37]	34 [31-37]	Cesarean section	Ketamine 10 mg	Saline solution	The primary outcome was the incidence of breakthrough pain in the first 24h. Secondary outcomes included the number of acetaminophen/hydrocodone tablets administered and NRS-11 for pain (0-10).
Behaeen K	2014	RCT	20	20	Middle East	22.5 ± 2.5	22.4 ± 1.77	Cesarean section	0.5 mg/kg ketamine	Saline solution	The first analgesic request, the amount of analgesic and the pain intensity.
Behdad S	2013	RCT	30	30	Middle East	27.4 ± 4.80	29.31 ± 5.41	Cesarean section	Ketamine (30 mg) + midazolam (1 mg = 2CC)	1 mg midazolam (2CC)	Pain scores at first, second and third hours after cesarean section operation, meperidine consumption,
Bilgen S	2012	RCT	140		Europe	31 ± 4	32 ± 4	Cesarean section	Ketamine 0.25, 0.5, or 1 mg kg(-1)	Saline solution	morphine consumption, and pain scores assessed with an NRS-11 scale (0-10) at 2, 6, 12, 18, 24, and 48 h postoperatively
Ghazi-Saidi	2002	RCT	27	26	Middle East	28.66 ± 5.25	27.07 ± 3.28	Cesarean section	0.2 mg/kg intravenous (IV) ketamine	Saline solution	Pain score, cumulative morphine consumption in 24 h.
Haliloglu M	2016	RCT	26	26	Europe	29.1 ± 2.2	29 ± 2.2	Cesarean section	a ketamine bolus of 0.5 mg kg(-1) IV was administered at the time of induction of general anesthesia. After induction, a ketamine infusion of 0.25 mg kg(-1) h(-1) was started and discontinued at the end of surgery.	Were given identical volumes of saline solution	Morphine consumption, NRS-11, rescue analgesia, and incidence of side effects.

Table 1 (cont.). *Baseline characteristics of included studies*

Author	Year	Design	Number in T	Number in C	Region	Age		Patient type	Treatment	Control	Outcomes
						Ketamine	Control				
Han SY	2013	RCT	20	20	Asia	32.7 ± 3.7	32.5 ± 3.6	Cesarean section	a 0.5 mg/kg ketamine bolus IV followed by 0.25 mg/kg/h continuous infusion during the operation	Saline solution	Postoperative pain (VAS).
Jaafarpour M	2017	RCT	92		Middle East	27.9 ± 1.6	26.5 ± 1.7	Cesarean section	Ketamine (0.25 mg/kg)	propofol (0.25 mg/kg), ketofol (25 mg ketamine plus 25 mg propofol) and placebo (saline solution)	VAS, complications after surgery.
Khezri MB	2016	RCT	90		Middle East	18-40	18-40	Cesarean section	Bupivacaine 10 mg combined with 0.1 mg/kg ketamine	bupivacaine 10 mg combined with 25 μg fentanyl in group F and bupivacaine 10 mg combined 0.5 mL distilled water in group P	The time to first analgesic request, analgesic requirement in the first 24 hours after surgery, sensory and motor blockade onset time, duration of sensory and motor blockade, and the incidence of adverse effects were recorded.
Khezri MB	2013	RCT	30	30	Middle East	27.22 ± 5.81	26.55 ± 6.05	Cesarean section	Bupivacaine 10 mg combined with 0.1 mg/kg ketamine	Bupivacaine 10 mg	The time to the first analgesic request, analgesic requirement in the first 24 hours after surgery, onset times of sensory and motor blockades, the durations of sensory and motor blockades, and the incidences of adverse effects.
Menkiti ID	2012	RCT	30	30	Africa	30.3 ± 4.0	29.8 ± 3.1	Cesarean section	Ketamine 0.15 mg/kg	Saline solution	Postoperative pain (VAS)
Nayar R	2009	RCT	20	20	Asia	23.3 ± 4.1	24.6 ± 4.3	Cesarean section	Ketamine	Thiopentone	Postoperative pain assessment (subjective) VAS scores, heart rate, blood pressure,
Ngan Kee WD	1997	RCT	20	20	Asia	NA	NA	Cesarean section	Ketamine 1 mg/kg	thiopental 4 mg/kg	morphine consumption, VAS pain scores,
Rahmanian M	2015	RCT	80	80	Middle East	27.4 ± 4.8	27.6 ± 4.4	Cesarean section	0.25 mg/kg ketamine	Saline solution	postoperative pain and its potential complications.

Table 1 (cont.). *Baseline characteristics of included studies*

Author	Year	Design	Number in T	Number in C	Region	Age		Patient type	Treatment	Control	Outcomes
						Ketamine	Control				
Reza FM	2010	RCT	30	30	Middle East	26.96 ± 5.1	27.33± 4.54	Cesarean section	0.5 mg/kg ketamine	Isotonic saline solution	Pain was assessed by the VAS at 2, 6, 12, and 24 hours postoperatively; the amount of morphine used, and side effects were recorded.
Sen S	2005	RCT	90		Europe	26.3 ± 5.3	27.1 ± 4.6	Cesarean section	Ketamine (0.15 mg kg(-1))	Saline solution	Arterial pressures, HR values, adverse effects, the time of first request for postoperative analgesia, VAS pain scores, total analgesic consumptions.
Senapathi TG	2016	RCT	18	18	Asia	28.9 ± 6.2	29.7 ± 5.9	Cesarean section	Ketamine 0.3 mg/kg (KET group)	NaCl 0.9%	C-reactive protein and neutrophil levels were measured preoperatively and postoperatively, Postoperative VAS pain score.
Suppa E	2012	RCT	28	28	Europe	34	33.54	Cesarean section	IV midazolam 0.02 mg/kg and S-ketamine 0.5 mg/kg intramuscular bolus 10 minutes after birth followed by a 2 μg/kg/min IV continuous infusion for 12 h.	Placebo	Morphine consumption at 4-8, 8-12, and 12-24 h, pain threshold,
Xu Y	2017	RCT	165	165	Asia	31 ± 4	32 ± 4	Parturient	0.25 mg/kg diluted to 10 mL with 0.9% saline solution	Saline solution	degree of depression, NRS-11 score of pain at 3 days and 6 weeks postpartum.

Abbreviations: C, control; NA, not available; T, treatment.

Meta-Analysis Results

Pain Score

A total of 12 articles included in this study presented the scores of pain after ketamine administration for patients who underwent cesarean section. As indicated by the heterogeneity test ($P < 0.01$, $I^2 = 95\%$), the random effect model was used. As shown in Fig. 4, the overall effect of ketamine on relieving pain was significantly better than that of control (MD, –1.10; 95% CI, –1.61 to –0.59; $P < 0.0001$). In addition, we performed another analysis based on the type of analgesia. The pain scores in the ketamine were reduced compared with control group (general anesthesia: MD, –2.49; 95% CI, –4.45, –0.53; $P = 0.01$; spinal anesthesia: MD, –0.79; 95% CI, –1.35, –0.22; $P = 0.007$).

Next we performed a subgroup analysis to determine whether the role of ketamine in reducing pain was influenced by different pain scoring systems. Nonetheless, similar results were observed irrespective of the pain score types (Fig. 5), and it was significant with regard to Visual Analog Scale (VAS) (MD, –0.94; 95% CI, –1.48 to –0.39; $P = 0.0007$), but not Numeric Rating Scale (NRS-11) (MD, –1.45; 95% CI, –4.43, 1.52; $P = 0.34$).

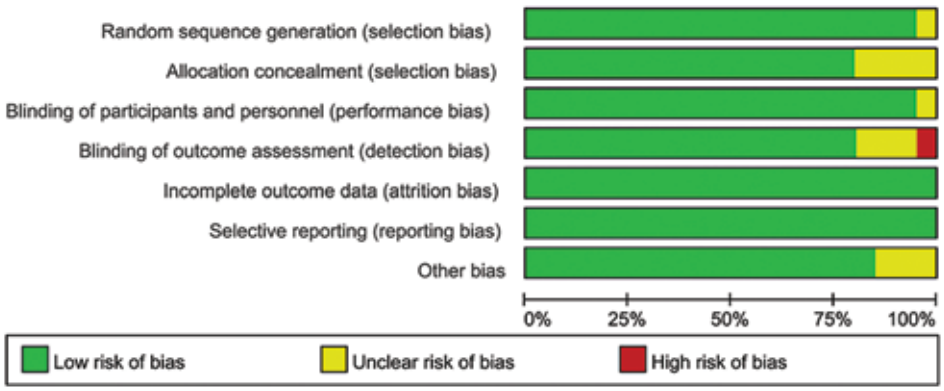

Fig. 2. *Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.*

Postoperative Analgesic Drugs Consumption

Morphine is commonly used for reducing pain postoperatively in clinical practice. The consumption of morphine reflects the extent of pain in patients with various diseases. Herein we also evaluated the impact of ketamine on morphine consumption after cesarean section. A total of 9 RCTs reported morphine consumption after cesarean section, and 6 RCTs presented consumption of other postoperative analgesic drugs. As illustrated in Fig. 6, the overall consumption of pain-relieving drugs was significantly reduced in the ketamine group as compared with the control group (MD, –10.12; 95% CI, –13.51 to –6.73; $P < 0.00001$). Furthermore, we performed another analysis based on the type of analgesia. The consumption of morphine in the ketamine was significantly reduced in the setting of spinal anesthesia but not general anesthesia when compared with control group (general anesthesia: MD –4.34; 95% CI, –8.80, 0.12; $P = 0.06$; spinal anesthesia: MD, –18.13; 95% CI, –24.14, –12.12; $P < 0.00001$). Subgroup analysis was conducted to evaluate if this effect of ketamine was independent of the drug types. The included studies were classified into 2 subgroups: morphine group and various analgesic agents group. The pooled results (Fig. 7) showed that the effect of ketamine on reducing the consumption of postoperative analgesic drugs was independent of the analgesic drug types. The mean reduction in morphine consumption was 6.11 mg (95% CI, 2.29-9.93; $P = 0.002$) and 35.46 mg (95% CI, 21.61-49.31; $P < 0.00001$) for other pain relief drugs.

Time to the First Analgesic Request

A total of 13 articles reported the time to the first analgesic request after surgery. The time extracted from individual studies was transformed into minutes. As shown in Fig. 8, the combined impact of ketamine on prolonging the time to the first analgesic request was significantly longer than that of the control group (MD, 72.48; 95% CI, 50.85-94.11; $P < 0.00001$). Based on analgesia type, the first time required for analgesia (general anesthesia: MD, 232.73; 95% CI, –54.61, 520.08; $P = 0.11$; spinal anesthesia: MD, 70.50; 95% CI, 49.20, 91.79; $P < 0.00001$) in the ketamine group were all improved than those of the control group. However, there was no significant difference between the ketamine group and control with regard to general anesthesia.

Heterogeneity Test and Publication Bias Test

Because of the significant heterogeneity among the included studies of the pain score, we explored the putative sources causing these differences. First, a sensitivity analysis was used to detect the studies that could be the main contributors of heterogeneity. Consequently, the studies by Rahmanian et al (24) and Xu et al (28) were deemed for exclusion (Fig. 9). However, after discarding these studies from the analysis of pain relief, the heterogeneity was still significant ($P < 0.01$). Therefore we performed meta-regression to further identify the potential sources of heterogeneity; 3 factors, year, pain score system, and pain measurement time point, were considered as the putative sources. However, the regression results (Supplemental Data S1)

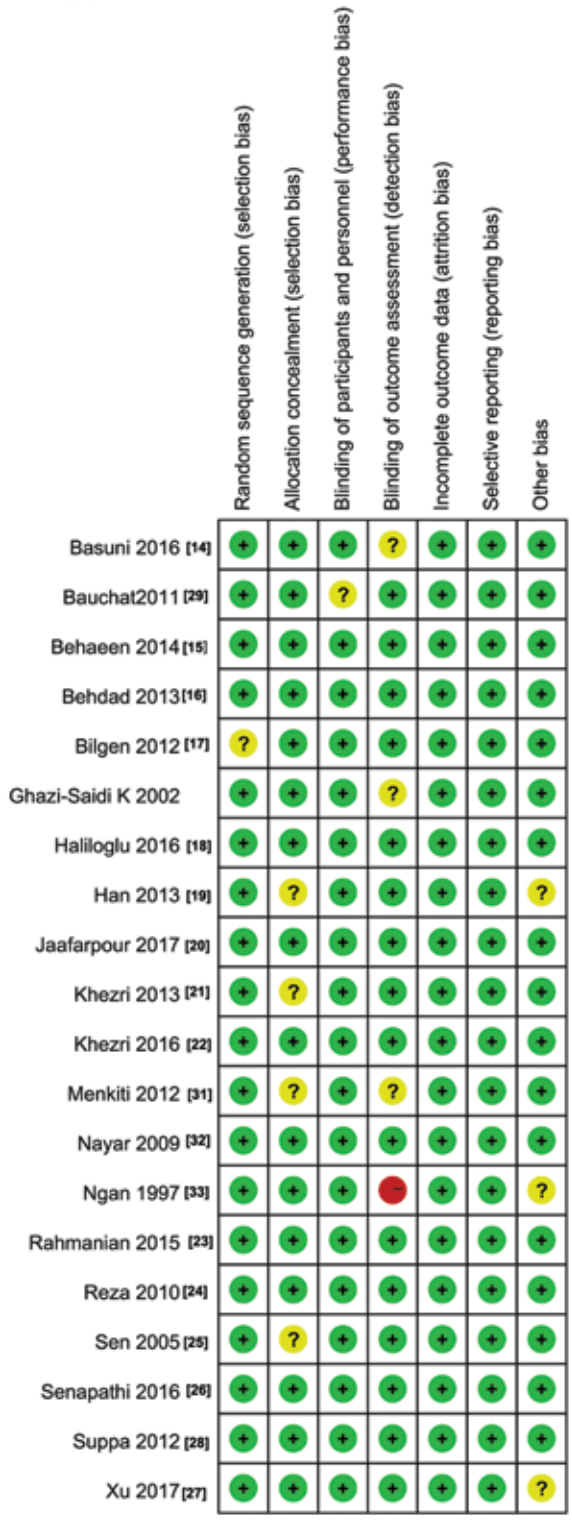

Fig. 3. *Risk of bias summary: review authors' judgments about each risk of bias item for each included study.*

did not suggest these factors to be the primary causes of heterogeneity ($P > 0.05$).

Moreover, publication bias analysis, Begg's test, Egger's test, and the funnel plot were used to present the results. The funnel plot and results of Begg's test (P = 0.047) and Egger's test ($P = 0.044$) indicated a significant publication bias (Fig. 10).

Discussion

Postoperative pain affects maternal rehabilitation. Also, painful stimulation is a major cause of postpartum depression, which necessitates postoperative analgesia. The pooled result suggested that the application of ketamine could decrease the pain score, reduce the consumption of postoperative analgesic drugs, and prolong the time to the first requirement of analgesics postsurgery. In addition, the pain relief effect of ketamine could be assessed irrespective of different kinds of pain evaluation methods. The decreased consumption of postoperative analgesic drugs by ketamine was independent of analgesic types.

In this study, the clinical efficacy of ketamine versus control was assessed systematically with respect to pain relief, postoperative analgesic drug consumption, and the time to the first request for analgesics. During the meta-analysis, significant heterogeneity was observed across the included studies. The sources of these differences might be various durations, doses of ketamine, outcome measurements, and reporting methods and baseline characteristics of the patients. For example, RCTs applied the VAS to evaluate the pain score, whereas others employed the NRS-11. To minimize the influence of these factors, the subgroup analysis was introduced. However, no significant heterogeneity was indicated by the I^2-statistic between the subgroups. Thus the differences in the treatment could be considered as responsible for the heterogeneity within the subgroup.

Some meta-analyses (13,35) assessed the effects of a local anesthetic agent on the postcesarean section pain. In 2009, Bamigboye et al (35) performed a meta-analysis to assess the impact of local anesthetic agent wound infiltration/irrigation and/or abdominal nerve blocks on the postcesarean pain. A total of 20 RCTs involving several anesthetic agents were included in the study, and the results demonstrated that adding ketamine to the local analgesia in women administered regional analgesia failed to confer any advantage. In 2015, another meta-analysis by Heesen et al (13) evaluated the desired and undesired effects of ketamine during cesarean section. The study included

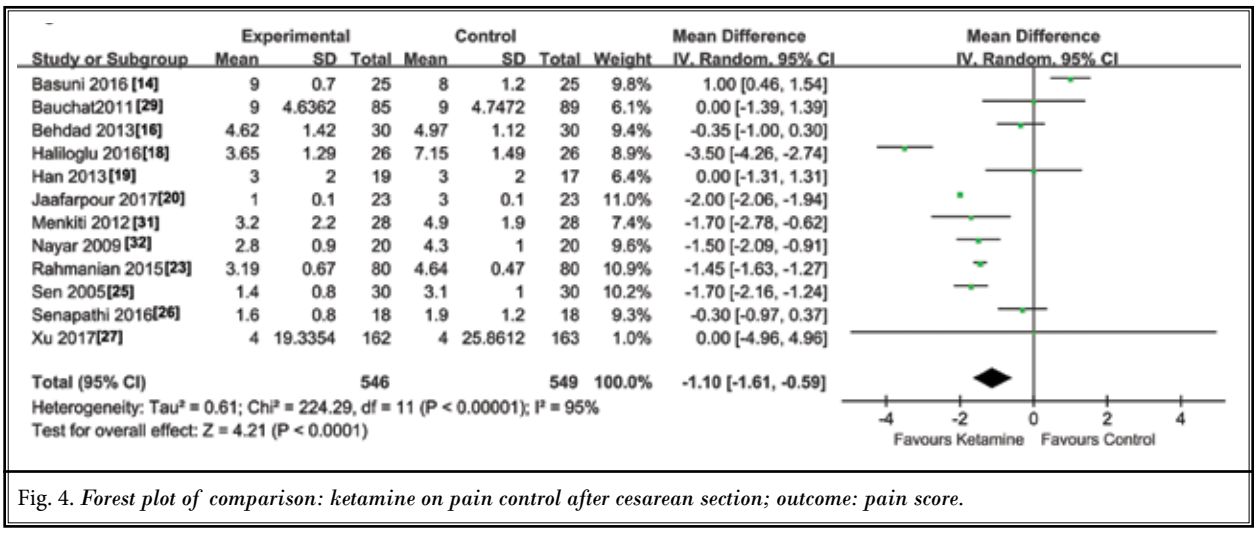

Fig. 4. *Forest plot of comparison: ketamine on pain control after cesarean section; outcome: pain score.*

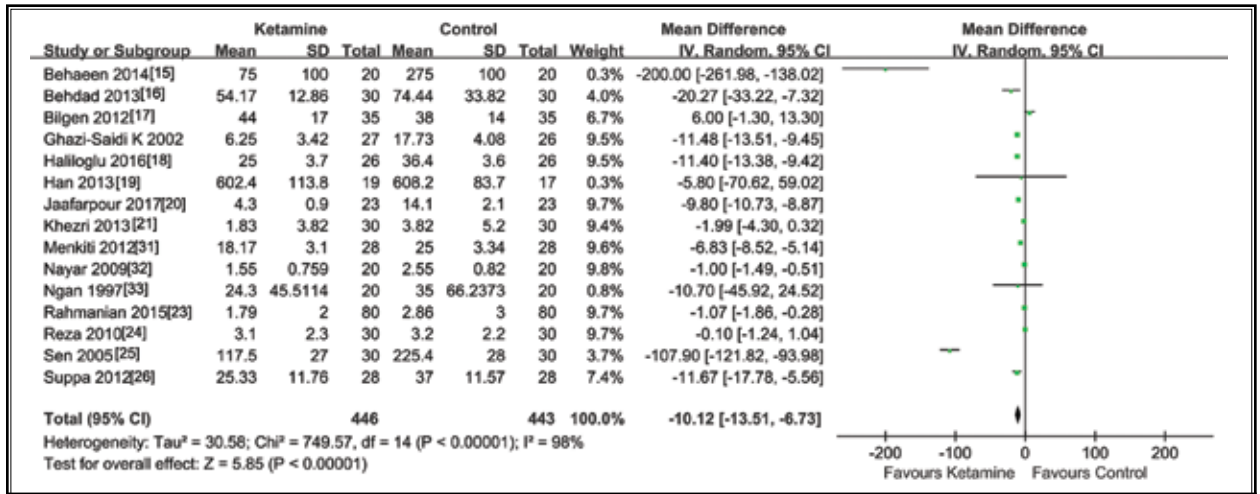

Fig. 5. *Forest plot of comparison: ketamine on pain control after cesarean section; outcome: pain score subgroup analysis.*

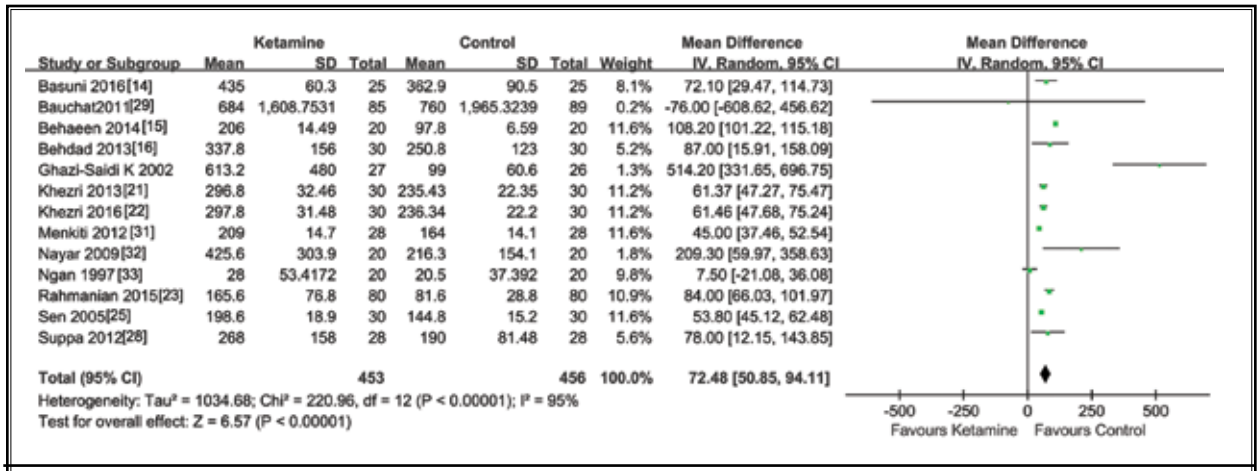

Fig. 6. *Forest plot of comparison: ketamine on pain control after cesarean section; outcome: postoperative analgesic drugs consumption.*

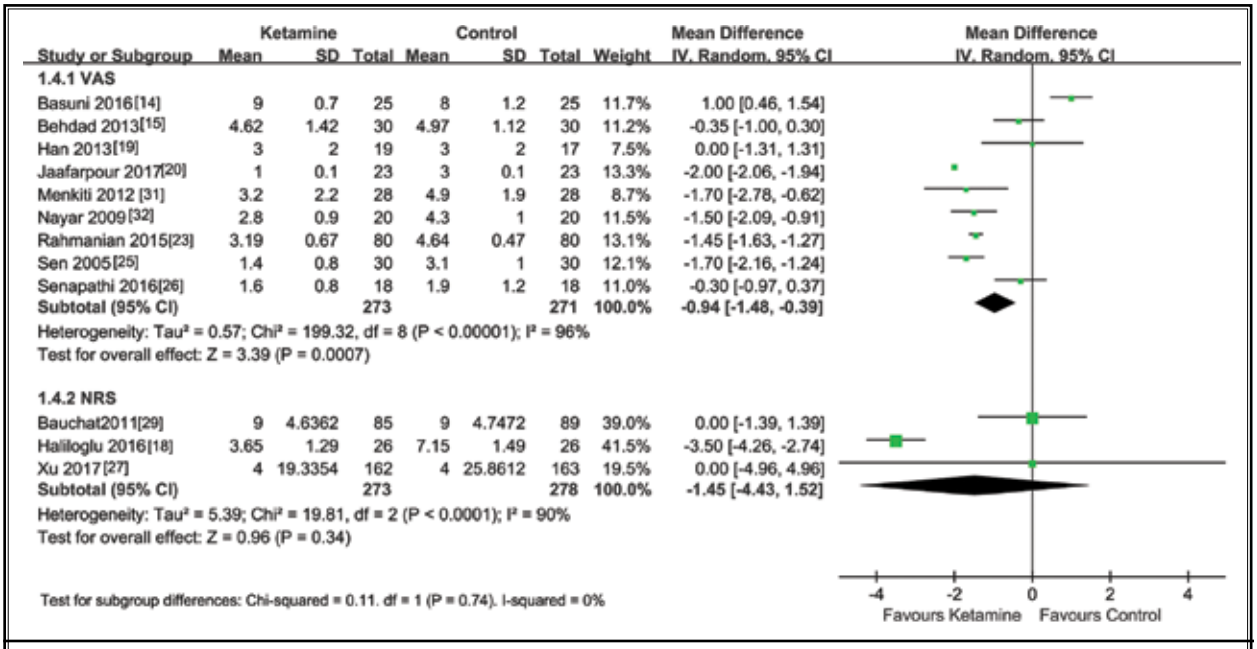

Fig. 7. *Forest plot of comparison: ketamine on pain control after cesarean section; outcome: postoperative analgesic drug consumption subgroup analysis.*

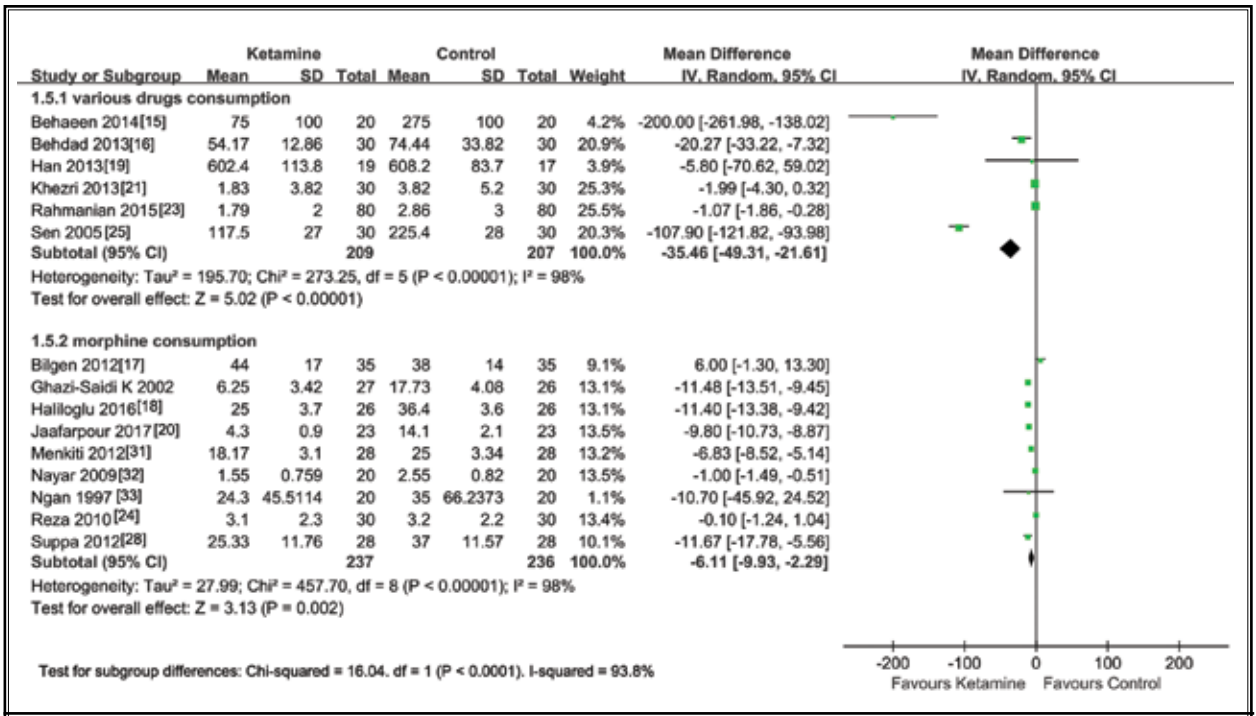

Fig. 8. *Forest plot of comparison: ketamine on pain control after cesarean section; outcome: time to the first request for analgesia.*

12 RCTs comprising 953 patients. The results showed that the VAS pain scores at rest after 2 hours postcesarean were significantly lower in ketamine-treated women along with a prolonged period to the first analgesic request (MD, 49.36 minutes; 95% CI, 43.31-55.41; $P < 0.05$), which was similar to the findings in the current study. Furthermore, we included advanced RCTs with a large number of patients, and found the duration to be 72.48 minutes ($P < 0.00001$).

In addition, we used subgroup analysis to strengthen our results and found a reliable effect of ketamine on pain management in women who had undergone a caesarean section. Meanwhile, it is worthy to note the incidence of the side effects of using ketamine. The side effects of ketamine include postoperative nausea and vomiting, hypotension, bradycardia, hallucination, sedation, and pruritus. Due to limited data about adverse events, the meta-analysis was not performed. Overall, the prevalence of postoperative nausea and vomiting, hypotension, bradycardia, and pruritus was reduced in the ketamine group compared with those in the control group. The number of patients with sedation or hallucination was increased in the ketamine group compared with control. Basuni (15) reported that 2 patients developed sedation in the ketamine group, whereas there was no incidence in the control group. The study of Rahmanian et al (24) reported that the proportion of patients with hallucination was 22.5% in the ketamine group, whereas it was 10% in the control group. These data suggest that ketamine exhibit good safety, even though the incidence of a few adverse events increased.

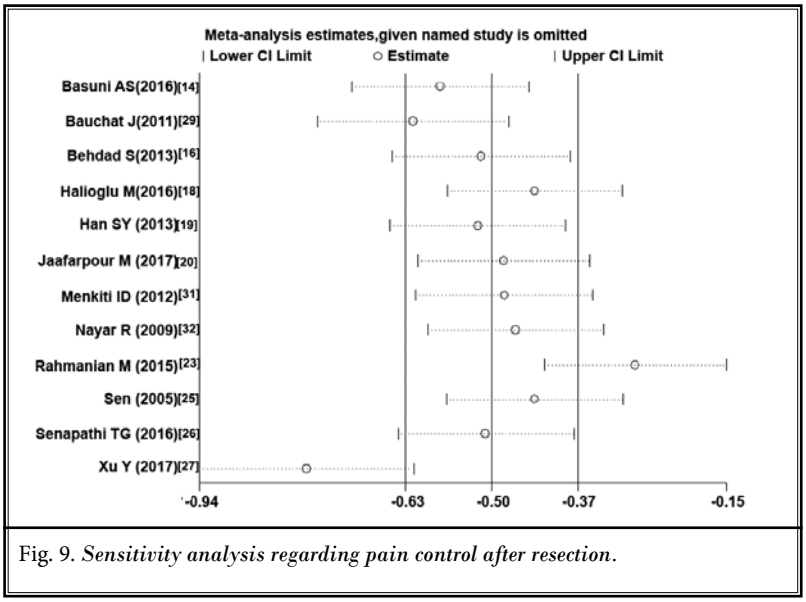

Fig. 9. *Sensitivity analysis regarding pain control after resection.*

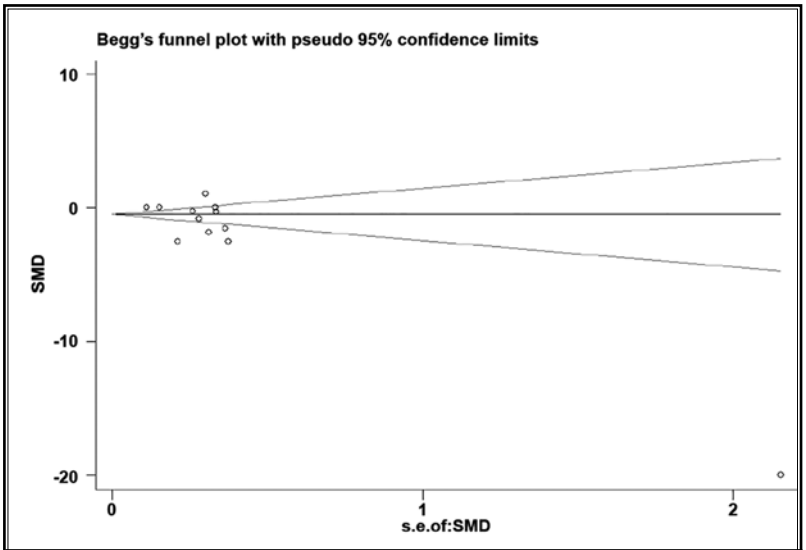

Fig. 10. *Funnel plot based on the data of pain control.*

Nevertheless, the present study had some limitations. First, the time and dose of ketamine administration differed across the included studies. None of the studies had reported the optimal clinical dose and time of ketamine. Second, the baseline characteristics of the patients were different, which might increase the heterogeneity of the included studies. The sample size was small, and the outcome measurement and reporting methods of the included studies were not identical. Third, only published articles and conference abstracts were included, which might increase the publication bias. However, the current study still provides reliable evidence supporting the use of ketamine during cesarean section.

Conclusions

Ketamine supplemented during cesarean section for spinal anesthesia reduced the pain degree, consumption of morphine, and prolonged the time to the first request for postoperative analgesia. However, large-scale, multicenter, high-quality, randomized, double-blind, clinical trials are required to verify the current findings.

For supplemental files, please go to www.painphysicianjournal.com

Supplemental Data S1. Meta-regression.

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