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REVIEW

The Relationship Between Perioperative Use of Esketamine and Postpartum Depression Risk: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Purpose: To determine whether perioperative esketamine use decreases the risk of postpartum depression (PPD).

Methods: Online search of PubMed, Web of Science, and Embase was conducted to identify relevant studies. Key words for search included, but were not limited to, postpartum depression, esketamine, and clinical trials. The mean and standard deviation of the Edinburgh Postnatal Depression Scale (EPDS) scores were extracted from the studies as primary parameters.

Results: The literature search identified 226 articles, of which 5 met the criteria and were enrolled in the study. In total, 886 patients in the studies were taken into analysis. The EPDS scores in the esketamine group were lower than those of the control group at the early stage of puerperium (WMD=−2.05, 95% CI: −3.77, −0.34, p=0.019), whereas there was no significant difference at the middle and later stages (WMD=−1.41, 95% CI: −2.86, 0.04, p=0.056). The sensitivity analyses indicated that the result for the early stage was stable, whereas it was unreliable for the middle and later stages. The results of the Egger's test indicated no publication bias.

Conclusion: Perioperative use of esketamine contributes to a lower risk of PPD at the early stage of puerperium but not at the middle and later stages. To further verify this conclusion, more high-quality studies are required.

Keywords: esketamine, postpartum depression, pregnant women, mental health

Introduction

Postpartum depression (PPD), one of the most common mental disorders in women, involves a series of physical, emotional, and psychological changes after childbirth.[1] The incidence of PPD was estimated to range from 12% to 17.7%.[2,3] The recurrence rate of a second pregnancy was reported to be a staggering proportion of about 40%.[4] PPD typically occurs within 4 post-childbirth weeks and can last throughout the puerperal period, sometimes lasting almost 3 years.[5] Untreated PPD is associated not only with impaired maternal physical health, frail psychological wellbeing, bad relationships, and risky behaviors, but also with infant outcomes, such as abnormal development of mental and physical health.[6] Although previous studies have identified several risk factors for PPD, such as psychosocial stressors, family and spousal support, income, and marriage, most of these risk factors are not modifiable.[7] Neuroregulatory techniques such as electroconvulsive therapy and transcranial magnetic stimulation are efficient at treating severe depression, but they add an additional economic burden.[8–10] In addition, prevention is more important than treatment.

Therefore, it is necessary to take effective measures to prevent PPD. Esketamine, the S-enantiomer of ketamine, has a strong affinity for the N-methyl-D-aspartate receptor. In the treatment of depression, esketamine not only rapidly improves the symptoms of patients and reduces suicidal intention, but also has fewer adverse reactions.[11–13] Recently,

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esketamine was used to treat PPD. A single dose of esketamine failed to improve the incidence of PPD within 4 weeks.[14] However, some studies have concluded that intraoperative esketamine decreases the morbidity of PPD.[15–17]

Given the role of esketamine in depression, it is potential to become a candidate for PPD prevention. However, the efficacy of esketamine for PPD prevention has not yet been determined. This study aimed to determine the role of esketamine in PPD prevention for parturients who underwent cesarean section. We hypothesized that perioperative use of esketamine would be helpful in decreasing the risk of PPD.

Methods

This study is in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement.[18] Ethical approval and informed consent were not obtained. The study was not registered, and the study protocol was not applicable.

Literature Search

PubMed, Web of Science and Embase were used to search for related publications on November 7, 2023. Key words including "esketamine", "depression", "postpartum", "clinical trial", and their synonyms and MeSH terms were combined to be the search strategy. Specific strategies are presented in Supplement 1. No language restrictions were applied. Retracted articles were not taken into consideration.

Inclusion and Exclusion Criteria

The criteria were determined prior to literature review. We enrolled randomized clinical trials (RCTs) on the relationship between perioperative esketamine use and PPD for parturients who underwent cesarean section. The exclusion criteria were no formal depression scales, no depression scores, prepartum depression, animal studies, abortion, and a follow-up duration of < 4 weeks. Low-quality studies (Jadad score<4) were omitted. However, the sample size in this study was not limited.

Literature Review and Data Extraction

Two independent investigators first screened the titles and abstracts, followed by the methods, results, and conclusions of the studies. Studies that did not meet the inclusion criteria or met the exclusion criteria were excluded. Disagreements between the investigators were discussed and rechecked by a third investigator who was blinded to the study plan. The decision was made based on the discussions of the three investigators.

The Jadad scale for randomized controlled trials was then used to evaluate study quality.[19] The evaluation was based on 4 aspects: randomization, randomization protection, blinding method, and description of missing cases. The Jadad score ranges from 0 to 7, and no less than 4 points is considered high quality. The risk of bias for the selected RCTs was assessed by the criteria of the Cochrane review group.[20] The scoring process was similar to that previously described.

Data extraction from the manuscripts was based on the PICOS principle, including the first author, publication year, intervention time and method, number of subjects in the esketamine group, number of subjects in the control group, psychiatric screening tools for PPD, follow-up duration, results of the PPD score, and study conclusion. Data were extracted from the manuscripts by two independent investigators and recorded in an Excel file. The third researcher was responsible for solving the disagreements regarding data extraction.

Data combinations and transformations were performed using online tools. Multiple groups of means and standard deviations (SD) were combined using a calculator at https://www.statstodo.com/CombineMeansSDs.php. Median and interquartile values were transformed to mean and SD using the Scenario 2 model at https://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html.

Primary Outcome

A decrease in the Edinburgh Postnatal Depression Scale (EPDS) score was observed among women who were administered esketamine in the perioperative period.

Meta-Analyses

Stata 12.0, and Review Manager 5.3 were used for the analyses. The mean and SD of the EPDS scores were reported for PPD risk evaluation. A significant effect requires that the weight mean difference (WMD) for continuous data is not equal to 0, and the confidence interval does not include 0. First, we conducted a heterogeneity test via Stata 12.0. The analysis model was selected based on the I-squared value. The random effect model was applied if I^2 was > 50%; otherwise, a fixed effect model was employed. Sensitivity analysis was conducted for significant heterogeneity. Egger's linear regression test was used to determine publication bias. The significance level was set at 0.05.

Results

The initial search totally screened out 226 articles, 218 of which were omitted after checking the inclusion and exclusion criteria. Finally, 5 articles with high quality (Jadad score > or = 4) were enrolled. Figure 1 shows the flow chart. A total of 886 patients from 5 RCTs were taken into analysis (Table 1).[14,21–24] The characteristics of the included studies are shown in Table 1. Table 2 shows the main results of the EPDS scores for the included studies.

Methodological Quality of Studies

The Jadad scores of the included studies ranged from 5 to 7, with a median of 6. Figure 2 and Supplement 2A show the results of the evaluation of the Cochrane Collaboration's risk of bias tool.[20] Two studies did not describe randomization generation or protection in detail. One study did not provide an appropriate blinding method. One study reported that

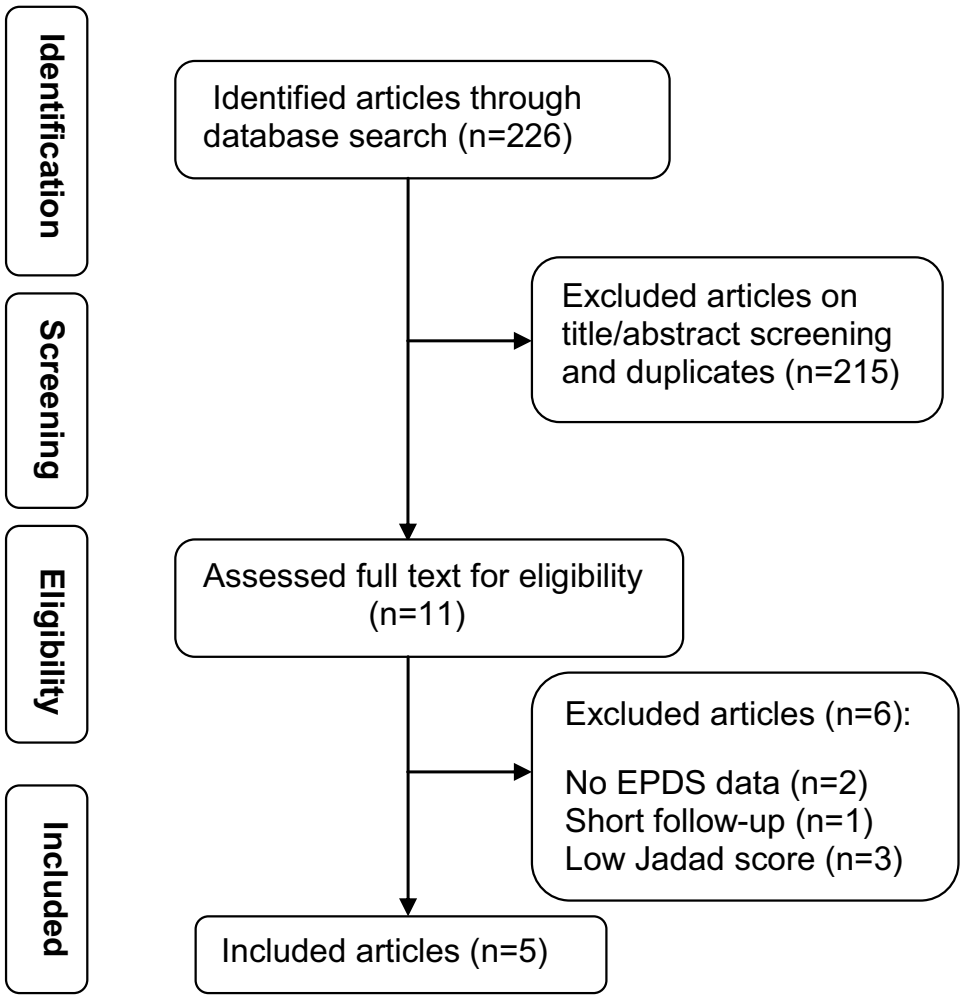

Figure 1 The flow chart of article enrollment.

Table 1 Characteristics of the Enrolled Studies

Author	Year	Intervention stage	Cases of Intervention/ control, n	Follow-up duration	PPD risk tool	Conclusion at endpoint
Wang	2023	Postoperative, PCIA	87/29	6 weeks	EPDS	Lower PPD risk in esketamine group
Liu	2023	Intraoperative, IV and postoperative, PCIA	62/61	6 months	EPDS	No lower PPD risk in esketamine group
Shen	2023	Intraoperative, IV	102/100	4 weeks	EPDS	No lower PPD risk in esketamine group
Guo	2023	Postoperative, PCIA	85/85	6 weeks	EPDS	No lower PPD risk in esketamine group
Han	2022	Postoperative, PCIA	122/153	4 weeks	EPDS	No lower PPD risk in esketamine group

Abbreviations: PCIA, intravenous patient-controlled analgesia; PPD, Postpartum depression; EPDS, Edinburgh Postnatal Depression Scale. IV, intravenous injection.

Table 2 EPDS Scores of the Included Studies

Study	N1	Mean1	SD1	N2	Mean2	SD2
3 or 7 days after delivery						
Wang 2023[21]	87	3.62	2.15	29	11.70	4.30
Liu 2023[22]	62	5.29	4.55	61	6.00	4.56
Shen 2023[14]	102	2.72	3.39	100	2.56	2.80
Guo 2023[23]	85	5.30	1.40	85	6.00	1.60
Han 2022[24]	122	6.00	2.47	153	7.56	3.14
4 or 6 weeks after delivery						
Wang 2023[21]	87	4.08	3.65	29	12.40	5.60
Liu 2023[22]	62	5.00	4.55	61	5.50	3.80
Shen 2023[14]	102	1.89	3.59	100	1.62	2.60
Guo 2023[23]	79	5.30	1.80	77	5.40	1.30
Han 2022[24]	122	7.15	2.92	153	7.55	2.50

Notes: n, number of subjects. 1, esketamine group. 2, control group. SD, standard deviation.

several subjects were lost to follow-up at the 42 post-delivery day, but the result does not describe it. One study did not provide the calculation of sample size. These studies were judged to have an unclear bias. Another study was determined to be at high risk owing to its high dropout rate and insufficient sample size to detect a significant difference.

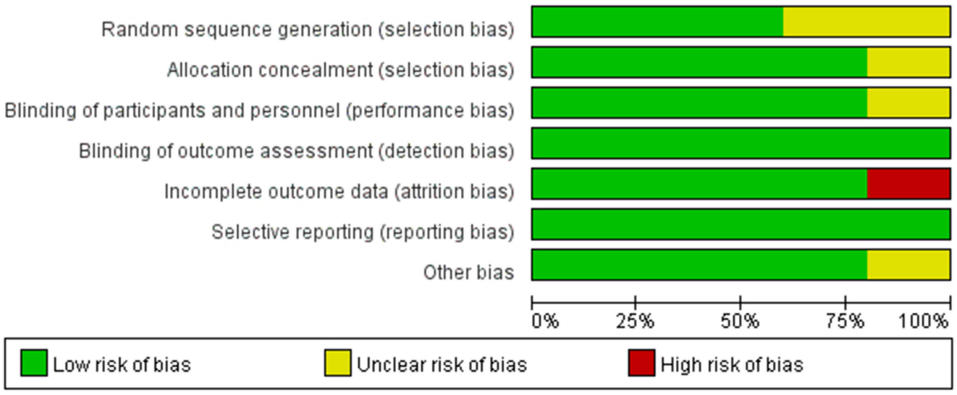

Figure 2 Risk of bias graph based on the Cochrane Collaboration's risk of bias tool.

Postpartum Depression Risk

The EPDS score in the esketamine group was 2.05 points (95% CI, −3.77, −0.34) lower than that in the control group at the early puerperium stage (p=0.019, Figure 3A). The I^2 value was 95.20%. The results of sensitivity analysis indicated that the combined effect was stable (Supplement 2B). The EPDS score in the esketamine group was 1.41 points (95% CI, −2.86, 0.04) lower than that of the control group at the middle and later stages of puerperium (p=0.056, Figure 3B). The I^2 value is 92.70%. However, sensitivity analysis indicated that the results were unreliable (Supplement 2C). The results of the Egger's test indicated no publication bias (Supplement 2D).

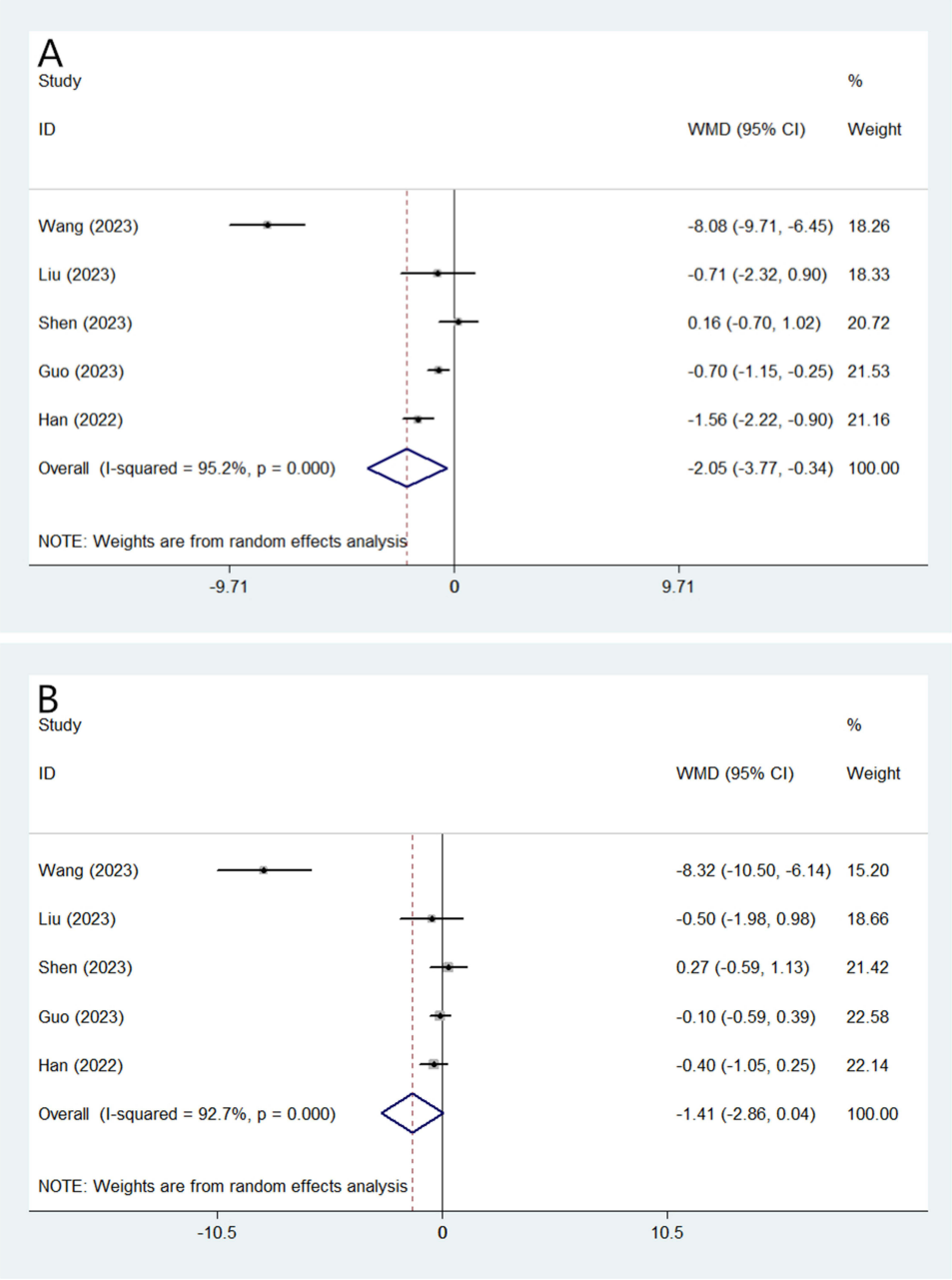

Figure 3 Forest plot of the relationship between esketamine and EPDS score for the early stage (**A**) and middle and later stages (**B**) of post-delivery.

Discussion

In the present study, we included 5 RCTs to analyze the relationship between the perioperative use of esketamine and PPD risk. The main findings indicated that esketamine was related to a reduced risk of PPD at the early stage of puerperium but not at the middle and later stages. Although some studies did not detect a significant difference in the EPDS scores between the esketamine and control groups at the early stage of puerperium, the synthetic effect was significant.

Since esketamine has higher efficiency and lighter adverse effects than that of ketamine, it has gained much attention of the anesthesiologists and psychiatrists.[25,26] Esketamine is a strong analgesic that has been used to provide assistant analgesia in intraoperative and postoperative practice, and is related to a reduced consumption of opioids.[27,28] Moreover, esketamine can be safely applied to caesarean section, since it does not impact on newborns.[29,30] Owing to its antidepressant effects, esketamine has been well recognized, especially for the treatment of resistant depression.[11,25] In addition, Yang et al[31] found that the intraoperative and postoperative use of esketamine was correlated with fewer postpartum depression symptoms and more remission of PPD for prenatal depression parturients.

Based on previous studies, esketamine may prevent PPD. This is important for both women and newborns. For non-depressed obstetrical patients, the potential administration methods of esketamine include intraoperative bolus and postoperative continuous infusion via intravenous patient-controlled analgesia (PCIA). Wang et al[21] conducted a study, in which esketamine (0.1, 0.2 or 0.4 mg/kg) was continuously infused via PCIA for 48h, and a lower EPDS score sustained to 6 post-delivery weeks. Similar results were observed at the early stage of postpartum in another two studies.[23,24] However, some evidence pointed out that perioperative use of esketamine did not have a significant influence on EPDS score at the middle and later periods of puerperium.[14,22–24] The present study showed that esketamine induced lower EPDS scores in the early stage of puerperium, but not in the middle or later stages. EPDS is an effective tool for predicting PPD and is frequently applied.[32,33] As a screening tool, a lower EPDS score is associated with a lower risk of PPD.

Although the half-life of esketamine is only approximately 3 h, the metabolite S-norketamine, which has a similar antidepressant effect to esketamine, survives much longer, which makes the antidepressant effect last for days.[34,35] These theories may explain the results of this study. However, lacking the diagnosis of a psychiatrist, some of the included studies failed to determine the incidence of PPD. Thus, we could not draw a conclusion regarding the relative risk of esketamine for the prevention of PPD.

The present study had some limitations. First, we excluded 2 studies without EPDS scores. As we did not obtain a response from the authors, we could not determine whether there were related data or the accessibility of the data. Considering that we compared the EPDS scores rather than the incidence of PPD, we had to abandon these 2 studies. Second, the checkpoints of EPDS were diverse in the studies, we merged the time points within 1 week into the early stage of puerperium and the time points at 4 and 6 weeks into the middle and later stages. In addition, studies on this topic are fledging and the number of eligible studies is limited. Therefore, subgroup analyses were not performed in this study. Further studies are needed, especially those reporting PPD incidence.

Conclusion

In summary, we found that the perioperative use of esketamine is helpful in decreasing the risk of PPD in the early stages of puerperium but not at the middle and later stages. More high-quality RCTs are urgently required to verify the conclusion.

Abbreviations

PPD, Postpartum depression; EPDS, Edinburgh Postnatal Depression Scale; WMD, Weight mean difference; CI, Confidence interval; WoS, Web of Science; RCTs, Randomized clinical trials; PCIA, Intravenous patient-controlled analgesia; IV, intravenous injection.

Data Sharing Statement

The data are provided in the Supplements, Figures, and Tables. No additional data is available for this study.

Ethics Approval and Consent to Participate

The approval of Ethics Committee and patient consent were not required.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no existing or potential conflicts of interest in this work.

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