ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2024 December 26; 12(36): 6864-6951

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

Contents

Thrice Monthly Volume 12 Number 36 December 26, 2024

EDITORIAL

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Study

Observational Study

World Journal of Clinical Cases

Thrice Monthly Volume 12 Number 36 December 26, 2024

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 12 Number 36 December 26, 2024

Contents

ABOUT COVER

Peer Reviewer of *World Journal of Clinical Cases*, Suman Baral, MD, Assistant Professor, Department of Surgery, Mediplus Hospital and Trauma Center, Pokhara 33700, Nepal. brylsuman.sur@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now abstracted and indexed in PubMed, PubMed Central, *Reference Citation Analysis*, China Science and Technology Journal Database, and Superstar Journals Database. The 2024 Edition of Journal Citation Reports® cites the 2023 journal impact factor (JIF) for *WJCC* as 1.0; JIF without journal self cites: 0.9; 5-year JIF: 1.1; JIF Rank: 168/325 in medicine, general and internal; JIF Quartile: Q3; and 5-year JIF Quartile: Q3.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

PUBLICATION DATE
December 26, 2024

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2024 December 26; 12(36): 6883-6886

DOI: 10.12998/wjcc.v12.i36.6883

ISSN 2307-8960 (online)

EDITORIAL

Merits and demerits of administering esketamine in preventing postpartum depression following cesarean section

Takahiko Nagamine

Specialty type: Pharmacology and pharmacy

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification
Scientific Quality: Grade D
Novelty: Grade C
Creativity or Innovation: Grade D
Scientific Significance: Grade C

P-Reviewer: Ge X

Received: August 14, 2024
Revised: September 1, 2024
Accepted: September 10, 2024
Published online: December 26, 2024
Processing time: 77 Days and 22.2 Hours

Takahiko Nagamine, Department of Psychiatric Internal Medicine, Sunlight Brain Research Center, Hofu 7470066, Yamaguchi, Japan

Corresponding author: Takahiko Nagamine, MD, PhD, Chief Doctor, Department of Psychiatric Internal Medicine, Sunlight Brain Research Center, 4-13-18 Jiyugaoka, Hofu, Yamaguchi, Hofu 7470066, Yamaguchi, Japan. anagamine@yahoo.co.jp

Abstract

Emergency cesarean section is associated with the development of postpartum depression. Esketamine has been demonstrated to have a rapid onset of antidepressant effects. Randomized controlled trials and meta-analyses have demonstrated the efficacy of esketamine in preventing postpartum depression after cesarean section. However, the data included in these analyses were derived from elective cesarean sections and differed in the dose and timing of esketamine administration. Esketamine is a dissociative anesthetic with a dose-dependent risk of inducing psychotic symptoms, including hallucinations. In the setting of cesarean section, esketamine should be administered with caution and only if the potential benefits outweigh the risks.

Key Words: Esketamine; Cesarean section; Depression; Adverse event; Medial prefrontal cortex

Core Tip: Emergency cesarean section is a risk factor for postpartum depression. Esketamine is effective in preventing postpartum depression after cesarean section. However, esketamine carries a risk of inducing psychotic symptoms, such as hallucinations and dissociation. The use of esketamine during cesarean section should be restricted to appropriate patients, taking into account its benefits and drawbacks.

Citation: Nagamine T. Merits and demerits of administering esketamine in preventing postpartum depression following cesarean section. *World J Clin Cases* 2024; 12(36): 6883-6886
URL: https://www.wjgnet.com/2307-8960/full/v12/i36/6883.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i36.6883

INTRODUCTION

Cesarean sections account for approximately 30% of annual births in developed countries, and emergency cesarean sections account for nearly 10% of all births[1]. Emergency cesarean sections can cause post-traumatic stress disorder in new mothers as a negative experience and are one of the important risk factors for postpartum depression[1]. Unlike most serotonergic antidepressants, esketamine has a rapid onset of antidepressant effects and may be effective in post-traumatic stress disorders[2]. Recently, attention has been focused on whether esketamine can prevent the development of postpartum depression associated with cesarean section.

EFFICACY OF ESKETAMINE IN CESAREAN SECTION: RANDOMIZED TRIALS

Randomized controlled trials have recently been conducted to evaluate the efficacy of esketamine for pain control during cesarean section and for preventing postpartum depression. I read with great interest the article by Chen *et al*[3] in this journal on the use of esketamine for pain management during cesarean section and prevention of postpartum depression. Their study design and results are as follows. A total of 315 women undergoing elective cesarean section under combined spinal-epidural anesthesia were randomized into three groups: Low-dose esketamine (0.15 mg/kg), high-dose esketamine (0.25 mg/kg), and control (saline). Compared with the control group, the low-dose and high-dose esketamine groups experienced less postoperative pain and reduced analgesic use. The Edinburgh Postnatal Depression Scale was significantly lower in the esketamine groups on the 2nd day and 7th day after cesarean section. However, the incidence of hallucinations, lethargy, and diplopia within 2 hours was statistically significantly higher in the esketamine groups than in the control group, and increased in a dose-dependent manner[3].

Other recent randomized control trials examining the efficacy of esketamine during cesarean section also found a preventive effect against postpartum depression, although the administration method of esketamine differed from that of Chen *et al*[3]. A randomized controlled trial of patient-controlled intravenous analgesia for pain management after cesarean section compared two groups, sufentanil 2 μg/kg (control group) and esketamine 1.5 mg/kg added to it (esketamine group), and found that the incidence of depression, as assessed by the Edinburgh Postnatal Depression Scale 42 days after cesarean section, was significantly reduced in the esketamine group (8.2% in the esketamine group *vs* 17.6% in the control group). The benefits of the esketamine group included a lower incidence of postpartum depression as well as reduced cumulative sufentanil consumption over the 48 hours after cesarean section without increasing the incidence of serious side effects[4]. In another randomized controlled trial, patients in the esketamine group received a single intravenous injection of 0.25 mg/kg esketamine immediately after delivery, followed by 50 mg esketamine as an adjunct to patient-administered intravenous analgesia for 48 hours after cesarean section, while patients in the control group received normal saline. The incidence of postpartum depression measured using the Edinburgh Postnatal Depression Scale 1 week after delivery was significantly lower in the esketamine group (23.0% in the esketamine group *vs* 35.3% in the control group), indicating that perioperative intravenous esketamine prevents early postpartum depression and that the antidepressant effect of esketamine is rapid[5]. Although the method and dosage of esketamine varied depending on the study design, randomized controlled trials have shown its effectiveness in controlling pain after cesarean section and preventing depression.

EFFICACY OF ESKETAMINE IN CESAREAN SECTION: META-ANALYSES

Next, we look at the results of several meta-analyses that pooled and analyzed clinical trials on the use of esketamine during cesarean section. Several meta-analyses have also been reported examining the preventive effect of esketamine on postpartum depression after cesarean section. A meta-analysis of the effects of esketamine during cesarean section from seven randomized trials involving 669 patients treated with esketamine and 619 control patients showed that the incidence of postpartum depression as measured by the Edinburgh Postnatal Depression Scale 42 days after cesarean section was significantly lower in the esketamine group without an increase in side effects[6]. In another meta-analysis for seven randomized controlled trials examining the Edinburgh Postnatal Depression Scale for cesarean section, the esketamine group had a significantly lower score than the control group from 1 week after cesarean section, and the relative risk (RR) of developing postnatal depression 4 weeks to 6 weeks after surgery was low at 0.48. However, the esketamine group had a significantly higher RR of developing hallucinations at 13.85[7]. A meta-analysis of 14 studies, including 12 randomized controlled trials and 2 retrospective cohorts, found that patients receiving esketamine had a lower incidence of postpartum depression 1 week [log odds ratio: -0.956 (95%CI: -1.420 to -0.491)] and 42 days (log odds ratio: -0.989 [95%CI: -1.707 to -0.272]) after cesarean section compared with controls. Furthermore, the Edinburgh Postnatal Depression Scale scores in the esketamine group were significantly lower than those in the control group during both the 1st week [Hedge's g: -0.682 (95%CI: -1.088 to -0.276)] and 42 days after caesarean section [Hedge's g: -0.614 (95%CI: -1.098 to -0.129)][8]. Yet another meta-analysis of eight randomized trials involving a total of 1655 participants found that esketamine reduced the incidence of postpartum depression by 48% (RR: 0.52, 95%CI: 0.35 to 0.79). However, for immediate intraoperative adverse reactions, the application of esketamine caused maternal nausea and vomiting (RR: 2.16, 95%CI: 1.22 to 3.81), dizziness (RR: 6.11, 95%CI: 1.49 to 24.98), and hallucinations (RR: 6.83, 95%CI: 1.57 to 29.68) compared to no esketamine use[9].

A summary of the results of these meta-analyses has shown that perioperative administration of esketamine during cesarean section exerts an antidepressant effect about 1 week after administration, and the effect lasts for 4 weeks to 6 weeks. However, all meta-analyses have noted the occurrence of transient central nervous system symptoms such as dizziness and nausea, as well as psychotic symptoms such as hallucinations.

ISSUES IN APPLYING RANDOMIZED CONTROLLED TRIALS AND META-ANALYSIS TO CLINICAL PRACTICE

In both randomized controlled trials and meta-analyses, the timing and dosage of esketamine vary from trial to trial, resulting in a lack of uniformity between trials. In order to determine the most effective administration method and dosage with the fewest side effects, dose-response studies and studies examining administration methods need to be conducted in advance. Secondly, all of the studies presented here used the Edinburgh Postnatal Depression Scale score to evaluate depression. This is certainly an excellent indicator of postnatal depression, with relatively good sensitivity and specificity, but it is a screening test for depression and does not take into account the severity of depression. This study included many patients with a low risk of depression who do not require esketamine administration. All of the studies presented here were conducted on elective cesarean sections, and further research is needed on emergency cesarean sections, which have a high risk of developing depression.

When using esketamine to prevent postpartum depression due to cesarean section, it is important to consider the adverse effects on mental function caused by the glutamatergic nervous system associated with childbirth. Therefore, in situations where an emergency cesarean section is necessary, the mother may not be able to express her needs and feelings. This leads to emotional trauma related to the birth experience[10]. Compared with elective cesarean sections, emergency cesarean sections are also associated with decreased breastfeeding, resulting in higher levels of depressive symptoms[11]. For mothers with emergency cesarean sections and breastfeeding problems, psychotherapeutic interventions that reduce the risk of early postpartum depressive symptoms without medication are also being promoted [11].

EFFECT OF ESKETAMINE ON THE CENTRAL NERVOUS SYSTEM

The effects of esketamine on the central nervous system are not fully understood. Because esketamine is an enantiomer of ketamine, results from pharmacological studies on ketamine can be inferred for the central actions of esketamine. Ketamine increases glutamate release from the medial prefrontal cortex (mPFC), which is involved in both antidepressant effects and the manifestation of psychotic symptoms[12]. The antidepressant effects of ketamine were abolished by selectively knocking down the GluN2B subunit of the N-methyl-d-aspartate (NMDA) receptor in gamma-aminobutyric acid (GABA) interneurons of the mPFC[13]. Ketamine is a NMDA receptor open channel blocker that preferentially inhibits the opening of NMDA receptors expressed on firing GABA interneurons, resulting in disinhibition and release of glutamate. Ketamine-induced increases in glutamate release in the mPFC activate postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors, which in turn open L-type voltage-dependent Ca^{2+} channels and induce activity-dependent brain-derived neurotrophic factor (BDNF) release, which is associated with rapid antidepressant effects[13]. Esketamine exhibits rapid and long-lasting antidepressant effects by enhancing glutamatergic neurotransmission and thereby affecting downstream neurotransmission, such as BDNF.

However, psychotic symptoms are a dose-dependent and common side effect of esketamine, but the mechanism of the side effects is not fully understood. Neurons work in synchrony to produce consciousness and perception. Esketamine is thought to inhibit excessive synchronization of neural circuits by blocking NMDA receptors, thereby disrupting patterns of neural activity and causing dissociative states[14]. Furthermore, when NMDA receptors are inhibited, neurons may in turn release excessive amounts of glutamate[15]. This excess glutamate disrupts the balance of other neurotransmitters and causes a dissociative state. Conversely, the blockade of NMDA receptors has been demonstrated to precipitate a state of dopamine dysregulation within the striatum and prefrontal regions, which in turn gives rise to the occurrence of psychotic symptoms such as excitement, dissociation, and hallucinations[16].

CONCLUSION

Randomized controlled trials and meta-analyses have shown that esketamine is effective in preventing postpartum depression after cesarean section. However, esketamine carries the risk of inducing psychotic symptoms such as hallucinations and dissociation. The use of esketamine during cesarean section should be limited to appropriate patients, taking into account its advantages and disadvantages. Perioperative use of esketamine in cesarean section is a double-edged sword.

FOOTNOTES

Author contributions: Nagamine T conceptualized the editorial and was solely responsible for the investigation, writing of the original draft, and all subsequent review and editing activities.

Conflict-of-interest statement: All authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Country of origin: Japan

ORCID number: Takahiko Nagamine 0000-0002-0690-6271.

S-Editor: Liu JH
L-Editor: Filipodia
P-Editor: Zhang L

REFERENCES

1 **Grisbrook MA**, Dewey D, Cuthbert C, McDonald S, Ntanda H, Giesbrecht GF, Letourneau N. Associations among Caesarean Section Birth, Post-Traumatic Stress, and Postpartum Depression Symptoms. *Int J Environ Res Public Health* 2022; **19** [PMID: 35457767 DOI: 10.3390/ijerph19084900]
2 **Nikayin S**, Murphy E, Krystal JH, Wilkinson ST. Long-term safety of ketamine and esketamine in treatment of depression. *Expert Opin Drug Saf* 2022; **21**: 777-787 [PMID: 35416105 DOI: 10.1080/14740338.2022.2066651]
3 **Chen HZ**, Gao Y, Li KK, An L, yan J, Li H, Zhang J. Effect of intraoperative injection of esketamine on postoperative analgesia and postoperative rehabilitation after cesarean section. *World J Clin Cases* 2024; **12**: 6195-6203 [DOI: 10.12998/wjcc.v12.i28.6195]
4 **Li S**, Zhuo Z, Li R, Guo K. Efficacy of esketamine for the treatment of postpartum depression and pain control following cesarean section: a randomized, double-blind, controlled clinical trial. *BMC Anesthesiol* 2024; **24**: 52 [PMID: 38321436 DOI: 10.1186/s12871-024-02436-6]
5 **Chen Y**, Guo Y, Wu H, Tang YJ, Sooranna SR, Zhang L, Chen T, Xie XY, Qiu LC, Wu XD. Perioperative Adjunctive Esketamine for Postpartum Depression Among Women Undergoing Elective Cesarean Delivery: A Randomized Clinical Trial. *JAMA Netw Open* 2024; **7**: e240953 [PMID: 38446480 DOI: 10.1001/jamanetworkopen.2024.0953]
6 **Wen Y**, Mao M, Wang X, Xu C, Shi X, Li P, Tian Z, Jiang M, Yuan H, Feng S. Efficacy and safety of perioperative application of esketamine on postpartum depression: A meta-analysis of randomized controlled studies. *Psychiatry Res* 2024; **333**: 115765 [PMID: 38330640 DOI: 10.1016/j.psychres.2024.115765]
7 **Nayyer MA**, Khan SM, Umer M, Imran H, Khalid S, Murtaza H, Sarfraz A, Atiq N, Rasool H, Fatima M. Efficacy and safety of peri-partum Esketamine for prevention of post-partum depression in women undergoing caesarian section: A meta-analysis and systematic review of randomized controlled trials. *Asian J Psychiatr* 2024; **97**: 104090 [PMID: 38820851 DOI: 10.1016/j.ajp.2024.104090]
8 **Parsaei M**, Hasehmi SM, Seyedmirzaei H, Cattarinussi G, Sambataro F, Brambilla P, Barone Y, Delvecchio G. Perioperative esketamine administration for prevention of postpartum depression after the cesarean section: A systematic review and meta-analysis. *J Affect Disord* 2024; **361**: 564-580 [PMID: 38925307 DOI: 10.1016/j.jad.2024.06.080]
9 **Ma B**, Tao X, Qi Y, Cao H, Cao Q, Zhou Z, Wang S. Effects of perioperative application of esketamine on postpartum depression in cesarean section: A systematic review and meta-analysis. *Medicine (Baltimore)* 2024; **103**: e38821 [PMID: 38968456 DOI: 10.1097/MD.0000000000038821]
10 **Deninotti J**, Denis A, Berdoulat É. Emergency C-section, maternal satisfaction and emotion regulation strategies: effects on PTSD and postpartum depression symptoms. *J Reprod Infant Psychol* 2020; **38**: 421-435 [PMID: 32683885 DOI: 10.1080/02646838.2020.1793308]
11 **Takács L**, Smolík F, Lacinová L, Daňsová P, Feng T, Mudrák J, Zábrodská K, Monk C. Emergency cesarean section is a risk factor for depressive symptoms when breastfeeding is limited. *J Psychosom Res* 2022; **153**: 110691 [PMID: 34999378 DOI: 10.1016/j.jpsychores.2021.110691]
12 **Moghaddam B**, Adams B, Verma A, Daly D. Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. *J Neurosci* 1997; **17**: 2921-2927 [PMID: 9092613 DOI: 10.1523/JNEUROSCI.17-08-02921.1997]
13 **Gerhard DM**, Pothula S, Liu RJ, Wu M, Li XY, Girgenti MJ, Taylor SR, Duman CH, Delpire E, Picciotto M, Wohleb ES, Duman RS. GABA interneurons are the cellular trigger for ketamine's rapid antidepressant actions. *J Clin Invest* 2020; **130**: 1336-1349 [PMID: 31743111 DOI: 10.1172/JCI130808]
14 **Matveychuk D**, Thomas RK, Swainson J, Khullar A, MacKay MA, Baker GB, Dursun SM. Ketamine as an antidepressant: overview of its mechanisms of action and potential predictive biomarkers. *Ther Adv Psychopharmacol* 2020; **10**: 2045125320916657 [PMID: 32440333 DOI: 10.1177/2045125320916657]
15 **Short B**, Fong J, Galvez V, Shelker W, Loo CK. Side-effects associated with ketamine use in depression: a systematic review. *Lancet Psychiatry* 2018; **5**: 65-78 [PMID: 28757132 DOI: 10.1016/S2215-0366(17)30272-9]
16 **Javitt DC**. Glutamate and schizophrenia: phencyclidine, N-methyl-D-aspartate receptors, and dopamine-glutamate interactions. *Int Rev Neurobiol* 2007; **78**: 69-108 [PMID: 17349858 DOI: 10.1016/S0074-7742(06)78003-5]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com