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EDITORIAL

Effect of esketamine on reducing postpartum pain and depression

Brandon Lucke-Wold, Armin Karamian

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Abstract

In this editorial, we comment on a recent article by Chen *et al*, that addressed the effect of intraoperative injection of esketamine on postoperative analgesia and postoperative rehabilitation after cesarean section. Poor management of post-cesarean pain is associated with decreased maternal care for the baby, longer hospitalization, and higher risk of developing postpartum depression. Esketamine is a more potent S-enantiomer of ketamine which has shown promising analgesic and antidepressant properties for managing post-cesarean pain and depression in clinical studies. However, due to its potential adverse effects on the neurological and hemodynamic status of patients, it is recommended that its usage in low doses should be limited to cesarean candidates experiencing unbearable pain. Before any recommendation for routine perioperative use of esketamine, more standardized clinical trials are needed to strengthen our existing knowledge of its effectiveness in reducing postpartum pain and depression.

Key Words: Cesarean section; Postpartum pain; Postpartum depression; Postoperative analgesia; Esketamine

Core Tip: In the last few years, esketamine has been suggested as a potential therapy for postpartum pain and depression, however, the available data are few. This editorial focuses on the recently published studies on the effectiveness of esketamine in relieving postpartum pain and postpartum depression symptoms. We hope that it will provide valuable information for the treatment of postpartum pain and depression.

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INTRODUCTION

In many countries, there has been a noticeable increase in cesarean deliveries in recent years, resulting in it being the most frequently performed surgical procedure. It has been reported that poor management of post-cesarean pain is associated with decreased breastfeeding quality, longer hospitalization, and higher risk of developing postpartum depression (PPD) [1]. High pain scores following cesarean surgery can also cause a delay in mobilization and caring for newborns[2]. According to Enhanced Recovery After Surgery guidelines, multimodal analgesia that includes regular nonsteroidal anti-inflammatory drugs and paracetamol is recommended for enhanced recovery from post-cesarean pain with moderate evidence level[3]. Ketamine is a commonly used pain reliever for reducing visceral traction pain during surgery, but there are concerns about its potential neonatal depression effects, neurotoxicity, and psychiatric symptoms[4]. Esketamine, an N-methyl-D-aspartate glutamate receptor antagonist, which is a more potent S-enantiomer of ketamine has demonstrated potential as an analgesic and antidepressant in managing postoperative pain and depression[5-7] and with a lower risk of psychiatric adverse events[8,9]. Recently, some studies have shown that perioperative or even postoperative administration of esketamine can be effective in reducing postoperative pain and the risk of postoperative depression in women undergoing cesarean surgery, without a significant increase in drug-related adverse events[7,10,11]. Additionally, it also reduces the need for opioid consumption following cesarean surgery[7,10,12]. Therefore, the best strategy would be to use a low dose of esketamine[10] to avoid the possible unfavorable side effects of the drug during or after surgery which can affect the recovery of the mother and the care of the baby. However, before any recommendation is made, more standardized clinical trials are needed to strengthen the existing knowledge.

EFFECTIVENESS OF ESKETAMINE IN REDUCING POSTPARTUM PAIN

In the study by Chen *et al*[13], 315 women undergoing elective cesarean surgery with combined spinal-epidural anesthesia were randomly divided into low-dose esketamine group (0.15 mg/kg), high-dose esketamine group (0.25 mg/kg), and control group (saline). Postoperative visual analog scale (VAS) scores were documented after surgery at 6, 12, 24, and 48 hours. Edinburgh postnatal depression scale (EPDS) scores were recorded at 2 days, 7 days, and 42 days. Ramsay sedation scores were also assessed at specified intervals post-injection.

In this study[13], compared to the control group, the low-dose and high-dose groups showed significant decreases in VAS scores 6, 12, and 24 hours after surgery ($P < 0.05$), however, during the first few hours following cesarean section there was no difference between high-dose and low-dose esketamine groups in the assessment of pain. In addition, the rescue analgesia rate within the initial 48 hours after surgery was significantly lower in both the low-dose and high-dose groups compared to the control group ($P < 0.05$). These results are consistent with a recently published multicenter, double-blind randomized clinical trial[14] on 600 women undergoing elective cesarean delivery, in which a single subanesthetic dose of esketamine (0.25 mg/kg) administered before the incision transiently relieved pain intensity compared to the placebo, based on the numeric rating scale (NRS) measurement approximately 10 minutes after esketamine administration ($P = 0.001$), but the difference between esketamine and placebo groups was not clinically meaningful. Contrary to the results of the study by Chen *et al*[13], the NRS pain score at other time points did not differ between esketamine and placebo groups in the study by Xu *et al*[14] although they used the same dose as the high-dose group in the study of Chen *et al*[13] and patients in both studies reached perfect analgesia with sensory block level at T4-T6. Overall, studies suggest that esketamine is associated with decreased intraoperative and postoperative pain following cesarean section, as well as with decreased opioid consumption[7,15-17].

In the study by Chen *et al*[13] in comparison to the control group, EPDS scores and rate of PPD were notably lower on 2 days and 7 days in low-dose and high-dose groups ($P < 0.05$), however, there was no significant difference between esketamine and control groups on postoperative day 42. In a randomized clinical trial conducted by Li *et al*[7] it was found that the incidence of PPD was lower in women who underwent cesarean section and received postoperative esketamine than in the control group on postoperative day 42 (8.2% *vs* 17.6%, $P = 0.02$). Differences between studies on the risk of PPD may be attributed to the dose of esketamine and the timing of drug administration, which may influence the long-term risk of depression. Therefore, although esketamine reduces the incidence of PPD, a contributor to depression, more studies are needed to determine whether the transient reduction in depression symptoms is due to the drug's antidepressant properties or its analgesic properties. An increasing amount of literature suggests that PPD is associated with higher serum high-sensitivity C-reactive protein and interleukin (IL)-6 levels and other inflammatory markers including tumor necrosis factor ligand superfamily member, hepatocyte growth factor, IL-18, fibroblast growth factor 23, and C-X-C motif chemokine 1[18,19]. Future studies should investigate the effects of esketamine on inflammatory markers levels and stress-related hormones after esketamine treatment to determine if there is a relationship between esketamine and reducing the occurrence of PPD.

In the study by Chen *et al*[13], Ramsay scores showed higher levels at 5 minutes, 15 minutes, and right after leaving the operating room following intravenous administration of esketamine in both low-dose and high-dose groups compared to the control group ($P < 0.05$). No significant difference was observed between the control and esketamine groups in terms of time to first flatus and defecation, whereas the time to ambulation was notably shorter in esketamine groups ($P < 0.05$). The authors also recorded adverse events post-surgery. Compared to the control group, the occurrence of hallucinations, drowsiness, and diplopia within 2 hours following esketamine injection was higher in both the low-dose and the high-dose groups ($P < 0.05$). The low-dose group experienced fewer rates of hallucination, lethargy, and diplopia in comparison to the high-dose group ($P < 0.05$). Rates of postoperative nausea, vomiting, and headache were similar between all three groups. In a multicenter, double-blind randomized clinical trial by Xu *et al*[14] during the intraoperative period, neurologic and mental symptoms were more common in patients who received esketamine compared to those given the placebo, however, the symptoms were transient and did not necessitate intervention. Additionally, more patients in esketamine group developed hypertension and tachycardia than in the placebo group. These findings indicate that adverse events following esketamine use, particularly at low doses, are usually transient and can be ignored, but close monitoring is still necessary for the initial hours after injection, especially for any serious hemodynamic changes.

There are some limitations to this study. In this study, it is not clear whether this study is double-blind or not, and the process of randomizing patients into low-dose, high-dose, and control groups is also unknown. More importantly, since esketamine can be passed to the infant through breastfeeding, this study did not examine the potential effects of esketamine on the cognitive and neurodevelopmental status of infants with long-term follow-up. Before recommending the routine use of esketamine in reducing postpartum pain, since there is no pre-defined definition for dosage, further studies with different doses and timing in populations from other countries should be conducted to increase the applicability of current findings, as most studies on the effectiveness of esketamine on postpartum pain and depression have focused on Chinese patients.

CONCLUSION

Esketamine is a promising drug in relieving postpartum pain and depression symptoms, however, its effects are transient. Due to its potential adverse effects on the neurological and hemodynamic status of patients, it is recommended that its usage in low doses should be limited to cesarean candidates experiencing unbearable pain. Before any recommendation for routine perioperative use of esketamine, further clinical trials are needed to increase the applicability of existing knowledge of its effectiveness in reducing postpartum pain and depression.

FOOTNOTES

Author contributions: Lucke-Wold B designed the overall concept and outline of the manuscript, and contributed to the discussion; Karamian A contributed to the discussion, writing, and editing of the manuscript and review of the literature.

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