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Ketamin in Prevention and Treatment of Postpartum Depression – Literature Review

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ABSTRACT

Introduction and purpose: Ketamine, used as an anesthetic and analgesic, has gained considerable attention in recent years in the context of treating various psychiatric disorders, particularly the treatment of drug-resistant depression. A promising application of ketamine appears to be the treatment of postpartum depression. According to the ICD-11 classification, postpartum depression is part of the disorder defined as major depressive disorder and is characterized by the onset of symptoms in the postpartum period, or 12 months after delivery. Conventional treatments for PPD involving both psychotherapy and pharmacotherapy, including non-selective serotonin reuptake inhibitors, may prove inadequate among some patients. ketamine acts on the NMDA receptor and affects the glutamatergic system, showing a significantly rapid antidepressant effect, compared to traditional antidepressants, which may prove crucial in the pharmacotherapy of patients whose response to conventional treatment has proved unsatisfactory. The purpose of this review paper is to present current research on the use of ketamine in the prevention of postpartum depression, including its mechanisms of action, the results of clinical trials to date, and the potential benefits and risks of its use in this specific group of patients.

Brief description of the state of knowledge: Both ketamine and esketamine are used in Poland in the pharmacotherapy of drug-resistant depression. In specialized psychiatric centers it is possible to use the drug off-label (ketamine) in the form of intravenous infusion. A therapeutic

option approved by the EMA and the Polish Office for Registration of Medicinal Products is esketamine in intranasal form. Currently, there are no clear recommendations in the context of the use of either substance in postpartum depression.

Summary: The number of new-onset depressive episodes, including postpartum depression, is growing in the world. The clinical condition of the patient affects many aspects of her life, especially the care of the newborn in the first weeks of the child's life. New therapeutic options are key to preventing PPD as well as achieving remission.

Material and methods: A comprehensive literature review was conducted using PubMed, focusing on articles and research papers published between 2020 and 2025

Keywords: postpartum depression, ketamine, esketamine, side effects, c-section, prevention

INTRODUCTION:

What is postpartum depression?

According to the latest ICD-11 classification, postpartum depression is classified as major depressive disorder, which occurs in the first year after childbirth, while corresponding to the relevant MDD criteria. The DSM-5 does not introduce a separate category for postpartum depression, treating it simply as major depression with onset during this specific period [1]. In the ICD-11, a depressive episode is defined as the simultaneous presence of at least five of a list of ten symptoms that must be present for most of the day, almost every day, for at least two weeks [2]. The ten symptoms include depressed mood, anhedonia, decreased ability to concentrate, pessimistic fixation about the future, belief in low self-esteem or excessive or inappropriate feelings of guilt, recurrent thoughts of death or suicidal thoughts/evidence of a suicide attempt, insomnia or excessive sleepiness, significant changes in appetite or weight, psychomotor agitation or slowing, and decreased energy or fatigue. It is necessary to establish one of these three criteria: anhedonia, lowered mood or markedly reduced interest. Symptoms may manifest as excessive irritability, tearfulness, lack of energy, problems concentrating, changes in sleep patterns, loss or excessive appetite, lack of interest in the newborn, difficulty interacting with the baby, presence of intrusive thoughts [3,4]. The incidence of PPD ranges

from 10-20% globally, reaching 26% in groups at higher risk; single motherhood, teenage motherhood, poor socioeconomic conditions [5]. Research findings suggest that PPD in developed countries reaches 9.5%, reaching 25.8% in low-developed countries [6]. Symptoms are usually evident from 4 to 6 weeks, but can occur up to 12 months postpartum [7]. We can distinguish a number of risk factors, including, but not limited to: delivery by cesarean section, unwanted pregnancy, domestic violence, lack of partner support, low socioeconomic status, vitamin D deficiency, previous depressive episodes, pregnant woman's age, negative experiences of previous pregnancies, or traumatic childbirth [8,9]. The occurrence of PPD in one pregnancy doubles the risk of an episode in subsequent pregnancies [4]. An episode typically lasts 3 to 9 months, and in the absence of medical intervention can persist for up to a year after delivery. Psychotherapy has had good results in treating mild to moderate episodes, with cognitive-behavioral or interpersonal therapy being the most commonly administered type of therapy [10]. Pharmacotherapy is mainly based on serotonin reuptake inhibitors (SSRIs), and serotonin and norepinephrine reuptake inhibitors [11].

Ketamine and esketamine

Ketamine and esketamine are substances that are used to treat depression, neuropathic pain, as well as in anesthesiology. Although both have a similar mechanism of action, they differ chemically and clinically. Ketamine is a mixture of two enantiomers (R and S), exhibits antagonistic noncompetitive activity against the NMDA receptor, and is widely used as an anesthetic agent [12]. A breakthrough discovery was the rapid antidepressant effect of ketamine compared to classical antidepressants, where in the case of the former compound, the antidepressant effect was evident just a few hours after administration of the drug [13]. Subsequent studies confirmed earlier reports of ketamine's rapid and effective action, marking its positive effects in the treatment of drug-resistant depression [14].

Esketamine is the S-enantiomer of ketamine, and shows similar pharmacodynamic properties as a non-selective, non-competitive NMDA receptor antagonist, with twice the receptor affinity of the enancjomery mixture [15]. Esketamine shows twice the affinity for the NMDA rec. compared to ketamine and three times higher if compared to the R-enantiomer [16,17].The mechanism of action of esketamine differs from traditional antidepressants, which mainly affect the serotonin system [18]. Studies suggest that esketamine may have a more rapid and pronounced benefit in treating depression in patients with suicidal thoughts, especially in the first few hours after administration, although the long-term effects on reducing suicide risk

require further study [19,20,21]. The SUSTAIN-2 study on the long-term use of esketamine showed that the improvements achieved during the initial phase of treatment were maintained in the long-term follow-up phase (control for 48 weeks), suggesting that esketamine may offer stable therapeutic benefits over the long term [22].

Potential of ketamine/esketamine in the prevention of PPD

Due to the use of ketamine in the induction of anesthesia in cesarean sections, the question has been raised as to whether, in addition to its anesthetic effect, its antidepressant properties might prove helpful in preventing the onset of postpartum depression. The 2020 study, conducted by a team of Iranian doctors, involved 134 women, separated into two groups; experimental and control, in a randomized fashion [23]. Before entering the study, the women answered questions about their age, education, number of previous pregnancies, socioeconomic status, and history of previous depressive episodes. Patients in group one received an anesthetic along with ketamine during the cesarean section procedure, while women in the control group received the anesthetic in combination with a placebo. The Edinburgh Postnatal Depression Scale (EPDS) was used to assess outcomes. These assessments were conducted twice after delivery, two and four weeks after cesarean section to see if ketamine had any effect on reducing the risk of postnatal depression. Women who received ketamine in combination with an anesthetic showed fewer depressive symptoms both two and four weeks after cesarean section compared to a control group that received a placebo [23].

Similar results were obtained in a study that this time used esketamine as an analgesic after cesarean section. A group of 380 patients was selected on the basis of criteria such as the age of the parturient between 18-45 years, gestational age between 36-42 weeks, pregnant weight BMI 17-36 kg/m2. Exclusion criteria were prenatal depression, previous experience of domestic violence, obstetric complications, illness and severe genetic defects of the fetus [24]. In the Control Group, of 190 patients, 166 received standard postoperative pain treatment, and the remaining 24 women had a change in delivery. In the experimental group, 161 women received the same treatment combined with the addition of esketamine at a dose of 0.5 mg/kg [24]. Due to the loss of contact with some patients, data analysis based on the EPDS questionnaire was performed on 153 patients in the control group and 122 in the experimental group. Patients were asked 10 questions from the EPDS on days 3, 14 and 28 postpartum. Results from 3 and 14 indicated significantly less severe depressive symptoms in patients in the experimental group compared to the other group. On postpartum day 28, the difference still persisted, but was not as significant as in the preceding follow ups. The escetamine was well

tolerated, and the number of side effects in the experimental group was not significantly different from the control group. There were no serious complications associated with its use. [24].

In both studies, we see a significant improvement in the mental state of patients in the experimental group compared to the control group. The use of ketamine intraoperatively as well as esketamine postoperatively for analgesia reduced the number of points the patients scored on the EPDS assessment [23,24].

Another study used ketamine, administered intraoperatively, intravenously, 5 minutes after the umbilical cord was severed. Study participants must have met the relevant inclusion criteria including, but not limited to:

- be between the ages of 20 and 40, planning a cesarean section, a term pregnancy (37-42 weeks), and the baby's birth weight had to be between 2,500 and 4,000 grams.

While at the same time the exclusion criteria were in effect, which included:

- previous history of burden of depression confirmed by psychiatric diagnosis, obstetric complications, chronic diseases, multiple pregnancies.

Pregnant women were divided into two groups, with one group receiving ketamine 0.25mg/kg in combination with 5 ml of 0.9% NaCl, and the other receiving placebo in the form of 5 ml of 0.9% NaCl. After administration of the drug, the incidence of dizziness, headache, and hallucinations was recorded. Due to the failure to meet certain criteria, change in the route of delivery, birth complications, refusal to participate in the study, and lack of contact, the final analysis involved 153 women in the experimental group and 152 in the control group, respectively. The analysis was based on the EPDS, with contact with patients one week, two weeks and four weeks after delivery. In addition, pain at the surgical site and pain associated with uterine contraction after two days were assessed. The group that received ketamine in addition to NaCl solution had a significantly lower incidence of depressive symptoms one week after delivery than the placebo group (22.6%), which was statistically significant. In contrast, there were no statistically significant differences in depressive symptoms between the groups after 2 weeks and after one month. In addition, postoperative pain on the NRS scale and sleep duration after 2 days were assessed. Among women in the experimental group, the incidence of dizziness was reported by 36.6% of subjects after ketamine, compared to 0% in the placebo group. Hallucinations occurred in 15.7% of patients in the ketamine group, compared to 0% of placebo [25].

We can find similar observations in a retrospective cohort study that aimed to evaluate the effect of low-dose esketamine on pain control after cesarean section and the risk of postpartum depression in women. The control group consisted of 132 women who were given sufentanil and palonosetron, while in the second group, patients received the same set of drugs in combination with ketamine. The experimental group was separated into two subgroups; low-dose ketamine ≤0.3 mg/kg, and high-dose >0.3 mg/kg. On the NRS scale, the esketamine group had significantly lower pain scores at each time point, that is, 2, 4, 8, 24 and 48 hours after cesarean section, compared to the control group. Moreover, patients in this group did not need significantly less morphine to abolish postoperative pain compared to women in the control group. In the context of PPD prevention, esketamine appeared to be effective, and EPDS scores within three months of delivery were significantly lower in the group taking the drug. Of the negative side effects, dizziness and nausea and vomiting were slightly more frequently reported than in the group that received standard opioid+setron treatment. Escetamine appeared to be effective in reducing postoperative pain and reducing the need for opioids after cesarean section, and showed a protective effect against postpartum depression, maintaining lower EPDS scores for three months. The higher dose did not have a significant effect on reducing the occurrence of postpartum depression symptoms, but may instead have increased the likelihood of side effects of the treatment used. Therefore, a low dose of esketamine may prove to be a safer option for women after cesarean section [26].

Other studies also indicate a beneficial effect of using a single dose of ketamine on preventing the onset of postpartum depression, where in the experimental group, symptoms occurred in 12.8% versus 19.6% of women in the control group [27]. Another positive aspect of the effect, may be a reduction in the intensity of suicidal thoughts [27,19].

Once the specific effects of ketamine and esketamine on PPD have been observed, selecting the appropriate dose of the drug is important in the process of potential treatment or prevention. In the study, which, as in those previously described, was designed to assess the occurrence of PPD and control of pain after cesarean section following ketamine, participants were assigned to four groups. One placebo group received only sufentanil at a dose of 1.5 μg/kg. The other groups were defined as L- low, M- medium, H- high, which corresponded to the doses of esketamine attached to the sufentanil treatment. Women in group L received the drug at a dose of 0.1mg/kg in addition to the opioid, group M- 0.2mh/kg, and the last group had the highest dose, or 0.4 mg/kg. The scheme for assessing the onset of PPD was similar, ESPD was used,

and follow up took place at weeks 1 and 6 of the study. In addition to the lower need for sufentanil among patients in the L,M,H groups compared to those in the control group, it was observed that 0% of patients in the H group showed PPD symptoms after the first week after delivery, and only 3.2% after 6 weeks. These results are quite significant, considering that in the placebo group, 30.2% of women reported symptoms of postpartum depression after 1 week after cc, and after 6 weeks it was 39.5%. Additionally, esketamine combined with an opioid reduced the subjects' need for a higher dose of opioid to relieve postpartum pain [28,26]. High-dose esketamine was most effective, but low doses also provided clinically significant benefits [28].

Based on the Food and Drug Administration's (FDA) 2019 approval of esketamine as a treatment for Major Depressive Disorder and Postpartum Depression the study's authors hypothesized that it could prove equally effective among pregnant patients in preventing PPD [29,30]. To this end, a group of 520 patients was selected, and the final analysis included 160 women from the control group and 159 from the experimental group. The division was done in a randomized manner. 201 patients were not included in the final analysis due to meeting the exclusion criteria and lost to follow up. Ketamine at a dose of 0.2 mg/kg was given only to women in the experimental group, the subjects in the other group received saline. The substance was administered within 40 minutes of follow-up. Follow-up, using the EPDS on day 4 after surgery showed that patients in the experimental group showed a lower incidence of PPD (13.8%), compared to women in the other group (23.1%). After 42 days, the effect of ketamine appeared to be negligible. As before, the results of the study showed a reduction in pain after ketamine, but side effects, in the form of dizziness, hallucinations and blurred vision, were more common in this group compared to women who received a placebo [30].

Conclusion:

Postpartum depression is a condition that affects not only the health of the mother, but also the health of the newborn. With the increasing number of cases of postpartum depression, and despite the extensive treatment options, including pharmacotherapy and psychotherapy, alternatives are still being sought that may prove more effective as treatments. Both ketamine and esketamine are potential compounds that could provide much benefit in the prevention and treatment of postpartum depression, primarily due to their rapid action. Clinical studies presented in the above paper suggest that these substances may reduce the need for pain medications during the postpartum period while reducing the severity of postpartum depression

symptoms. Nevertheless, this requires further research in order to analyze the safety and long-term effects of using ketamine and esketamine in this particular group of patients.

Disclosure:

Author's contribution:

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