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Invited Commentary | Anesthesiology

Routine Prophylactic Esketamine for the Prevention of Maternal Pain During Cesarean Delivery

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Neuraxial anesthesia is the gold standard for cesarean delivery and is associated with reduced maternal morbidity. However, neuraxial blockade may occasionally fail or be inadequate, with the onset of pain and distress for the mother leading to a suboptimal birthing experience and the potential for long-term psychological sequelae. Recognition of this challenging situation has led to clinical guidelines suggesting that ketamine (an *N*-methyl-D-aspartate inhibitor and nonopioid analgesic) may be a useful adjuvant in the management of an inadequate block during cesarean birth.[1] The more potent S-isomer, esketamine, may have a preferable psychoactive profile, making it potentially useful in this context; however, concerns regarding the potential detrimental neurologic and psychoactive effects of these agents may limit their use.

Xu et al[2] report findings from a multicenter randomized clinical trial (RCT) of 600 patients across 5 centers in China investigating the analgesic and sedative effects of subanesthetic doses of a routine, single, intravenous bolus of esketamine before commencing elective cesarean delivery with epidural anesthesia on pain and sedation scores. Notably, the trial design dictated that the study drug was administered before skin incision and therefore regardless of whether any breakthrough pain was experienced by the mother. The authors report no clinically significant difference in numeric rating scale (NRS) pain scores at any of the 8 prespecified time points, which ranged from immediately through 12 hours (median difference in NRS scores, 0; 95% CI, 0-0). In contrast, median (IQR) sedation scores were significantly increased during the operative period (2 [2-2] in the placebo group vs vs 4 [3-4] in the esketamine group), suggesting that mothers were "light asleep but responding to touch or pain." Placental transfer of esketamine was evident in the small subsample (n = 13) of neonatal blood samples, yet neonatal outcomes (Apgar scores and acid-base status) were similar between the groups. Most strikingly, 97.7% of women receiving esketamine experienced psychoactive symptoms (somnolence, vertigo, dizziness, hypertonia, daymares, and hallucinations), and 67.3% experienced nystagmus during the operative period. Rates of postoperative nausea and vomiting were also higher in the esketamine group on the first postoperative day, though there was no difference in psychoactive symptoms at that time point.[2]

There are few studies with which to compare these findings. A meta-analysis[3] of 20 RCTs (1737 patients) assessing the more commonly used racemic ketamine during cesarean delivery reported decreased postoperative pain and analgesia use, although the effect on intraoperative pain was not reported. Studies investigating the use of esketamine are even scarcer, with only 4 RCTs (n = 56-210) examining the role of systemic esketamine for cesarean pain but with substantially different study designs, primary outcomes, and esketamine doses.[4-7] Overall, the studies are, however, promising, suggesting that esketamine is associated with reduced intraoperative pain, reduced postoperative pain, and the need for lower doses of local anesthetic for spinal anesthesia. Two of the studies[6,7] also considered postnatal depression given the increasing recognition of esketamine as an effective treatment for depression, but the effects here were nonconsistent, potentially reflecting the short period of use. Only 1 study[4] assessed intraoperative pain and neonatal outcomes, reporting that esketamine was associated with reduced rates of visceral traction discomfort in the esketamine group (7.5% vs 45%, $P < .001$), without an increase in adverse neonatal effects. Consistent with the critical adverse outcomes reported by Xu et al, 3 of the 4 studies[4,5,7] noted increased psychoactive effects in the esketamine groups.

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Although we acknowledge that the trial by Xu and colleagues[2] was randomized and double-blinded with allocation concealment, several significant limitations merit further discussion. The use of epidural rather than spinal anesthesia is unusual in the context of elective cesarean birth in many developed countries, including the US and the UK, and the more commonly used spinal anesthesia is known to have faster onset, fewer complications, and lower intraoperative analgesic supplementation rates compared with de novo epidural. Exclusion of women with a body mass index (calculated as weight in kilograms divided by height in meters squared) of 27 or greater affects generalizability, removing a subpopulation with a higher incidence of adverse perioperative events, and is not representative of the obstetric population in many countries. Although neuraxial blockade was assessed using sensory testing to T4 to T6 levels, testing of motor blockade was not documented. Despite this, the almost perfect intraoperative pain scores in the control group suggest adequate block was attained but, most importantly, completely negates any potential for the administration of esketamine to improve pain scores. Furthermore, study power was based on a mean difference of 0.3 in NRS pain score (SDs of 0.85 to 1.23), arguably a difference of dubious clinical significance. Sampling of fetal blood for esketamine levels was performed in only a small subgroup of patients, and no longer-term follow-up was performed to assess any neurodevelopmental effects. Last, whether these psychoactive symptoms had any detrimental effects on the birth experience and conventional positive memories that can usually be generated at the time of an elective planned cesarean birth was not explored.

The reader should be left with no doubt that the routine use of a single prophylactic intravenous injection of esketamine (0.25 mg/kg) is not useful in reducing intraoperative or postoperative pain scores and is associated with a large proportion of mothers having short-term adverse neurologic sequelae. However, the important questions of whether esketamine is a useful adjuvant for mothers experiencing breakthrough pain, can contribute to the management of chronic postcesarean pain, or affects the risk of postnatal depression remain unanswered. Given the need for effective adjuvants for pain at cesarean birth and the ongoing opioid pandemic, future studies may wish to assess esketamine in varying doses and at different time points. We suggest that researchers undertake these studies in select populations with breakthrough pain, with a particular focus not only on any analgesic effects and neonatal and childhood outcomes but also on the neurologic and psychoactive symptoms that may alter a mother's lasting memory of childbirth.

ARTICLE INFORMATION

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