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Comments on "The Effect of Low-dose Ketamine on Post-caesarean Delivery Analgesia after Spinal Anesthesia"

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LETTERS TO EDITORS

We found the recent original article published in the Korean Journal of Pain by Seung Yeup Han et al., entitled "The effect of low-dose ketamine on post-caesarean delivery analgesia after spinal anesthesia" [1]. The authors expertly detailed an interesting investigation about the prophylactic administration of low-dose intravenous ketamine for reducing postoperative pain and postoperative opioid requirement in patients receiving intravenous fentanyl with patient-controlled analgesia (PCA) after caesarean section. They concluded that "Intraoperative low-dose ketamine did not have a preemptive analgesic effect and was not effective as an adjuvant to reduce postoperative pain score or opioid requirement in parturients receiving intravenous fentanyl with PCA following caesarean section." While this topic is a hot issue in anesthesia and pain medicine, it seems there are some concerns in the methodology of this study that undermine the ability of the reported data to lead to a definite conclusion. Here we note some comments on different points:

(1) Accurate estimation of the number of cases is one of the most important points in trial studies. The number of cases in this study was not estimated correctly, and the authors of the mentioned study should estimate the "power" of their study in order to compensate for any refusal of data. We can concede that if differences between their study groups (Ketamine group and controls) were not significant during follow-ups, it could be because of the small sample size.

(2) In clinical studies, randomization is extremely conclusive and crucial. The authors in this case did not report the method of their randomization (e.g., computer-based table of randomization or other). Therefore, it is not clear whether the two study groups in their study were randomized homologically or not.

(3) The authors followed their patients at 2, 6, 24, and 48 h after surgery. Therefore, their study is a prospective clinical trial, but it suffers from the lack of a participation flow diagram. There is no accompanying CONSORT (Consolidated Standards of Reporting Trials) [2,3] fellow chart to provide details on how many parturients declined consent as well as on the overall progress of the participants through the study. The authors affirmed that they enrolled

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a total of 40 parturients of American Society of Anesthesiologists (ASA) classes I and II undergoing cesarean section in their study and they excluded those parturients who had difficulties communicating, psychological disease, inflammation in the spinal puncture area, etc. However, in the analysis of data, the authors declared that one parturient in the experimental group and three in the control group were excluded due to a switch to general anesthesia or failed spinal puncture. This raises two questions: first, why the exclusion criteria were noted differently in the results section compared to the notes in the methods section, and second, how many patients were lost to follow-up during the study. These points should be stated with more clarity.

(4) On the other hand, the exclusion criteria seem to be inadequate for this topic. The authors did not report whether or not they excluded women with a history of malignant hyperthermia [4], hypersensitivity, sensitivity to parabens, and the use of vasoconstrictors which decrease systemic absorption of anesthetic agents [5]. Therefore, the mentioned criteria should be considered by the authors.

(5) The authors randomized the patients into the three studied groups and no significant differences in terms of age were reported. However, race, parity, comorbidities, occupation, age of menopause, menopausal hormone therapy, OCP use [6], etc. should be distributed equally among the three groups before any conclusions are drawn. Crucially, there is no mention of these criteria being recorded, nor are they reported in the results section. Thus one cannot be reassured that the studied groups are balanced for these crucial characteristics.

(6) In our opinion, the adverse effects of ketamine such as anxiety, bradycardia, chills, edema, drowsiness, hypotension [7], etc. need to be considered by the authors. Generally, the use of ketamine increases the adverse effects which were mentioned previously, and it is a very crucial consideration if there is any possibility of deducing these effects. Additional research is needed in this field.

In conclusion, the mentioned study certainly added evidence to the present literature, and revealed that intraoperative low-dose ketamine did not have a preemptive analgesic effect. Obviously, large-scale clinical trials employing accurate and powerful methods according to the CONSORT Statement and a homogeneous sample with well characterized controls and cases that increase the sensitivity of detecting the associations are required for this topic.

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