

Peer Review File

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Reviewer A

Comment 1: Sedoanalgesia is the practice of combining sedation with local anesthesia, usually in the case of surgery. Your case report is mainly about the systemic use of ketamine and not local anesthesia. Consider changing the term.

Reply 1: *We thank the Reviewer for noting this aspect. Following the Reviewer's suggestion, we replaced sedoanalgesia and correlated words by sedation plus analgesia, including in title and keywords.*

Changes in the text: The entire text was modified.

Comment 2: There are numerous grammatical errors that affect the interpretation of your report.

Reply 2: *We thank the Reviewer for his/her generosity to note these multiple misspellings, which were all corrected. This prompted the obvious need to carefully review the full MS, which led to the correction of several other grammatical errors throughout the text.*

Reviewer B

Thank you for the timely and important report.

When considering a revised version of your ms. would you please address the following points?

Comment 1: 1) Please comment on the possibility that the 'abstinence syndrome' was not due to ketamine but rather a return to pre-ketamine behaviors of the child.

Reply 2: *We thank the Reviewer for this remark. In fact, this issue was included in our questions. To exclude such hypothesis, a structured questionnaire was applied to the mother of the infant, confirming the language, learning, and cognition profile before hospitalization. To clarify this issue, the information was added to the revised MS, as below.*

Changes in the text: *"Furthermore, the structured questionnaire completed by the mother before the hospitalization confirmed that the infant had adequate cognitive and language skills, suggesting that such blunted domains observed after hospital discharge did not consist of the pre-ketamine behaviors of the child. "(pg 10, lines 210-213).*

Comment 2: 2) Was the WAT assessment done during the Day 1-7? If so, what are the values?

Reply 2: *We very much thank the Reviewer for requesting this clarification. Considering that WAT-1 challenge consists of an abstinence syndrome evaluation tool, the protocol of procedures suggests that WAT-1 may be applied immediately after*

sedoanalgesic weaning. Thus, we did not perform the WAT-1 test on the D1-D7.

Comment 3: 3) A related question is related to the documented state of the child prior to admission – please assure the reader that the neurocognitive changes reported were changes and not a continued manifestation of prior neurocognitive insufficiency.

Reply 3: *As commented above in the comment 1, this relevant issue was controlled by the authors through a structured questionnaire applied by the pediatric psychologist to the mother, collecting the cognitive domains of the infant at home, prior to the admission.*

Comment 4: 4) How can you ensure us that the non-ketamine medications did not contribute to the post-follow-up assessment (20 days after release) findings – e.g., walking, talking, etc? The big question being how can you assure us that ketamine was the primary or only medicine that induced these longer-term changes?

Reply 4: *We thank the Reviewer for noting this relevant aspect. This project emerged after observations of peculiar behaviors of some children after ICU discharge by clinicians. Unfortunately, when these children reached physiological homeostasis, they received hospitalization discharge with loss of clinical post-discharge evaluation. Indeed, cognitive assessment were not performed. The present case report presented the behavioral/cognitive symptoms hardly characteristic of the silent suspicious of neurotoxicological effects resulted from sedoanalgesic procedure that elicited two outcomes. Firstly, the infant was followed by the multidisciplinary team, even after hospital discharge; second, this intriguing case report triggered the elaboration of a cohort clinical study in the ICU service, which is in the phase of sample collection. However, our hypothesis of ketamine effects as the principal neurobehavioral impairments is based on the pharmacodynamic of each drug administered, which scarce studies of ketamine, mainly in animals, have pointed to this neurotoxicological damages. The mechanism of action of the other anesthetic agents administered in the infant did not justify the long-term effects observed in the infant. Thus, we discussed this issue in the discussion section (pg 8-9).*