Author’s response to reviews

Title: Increased Minimum Alveolar Concentration-Awake of Sevoflurane in Women of Breast Surgery with Sleep Disorders

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Reviewer 1

The manuscript was well reviewed. The major concerns as followings,

1. What is your purpose? For preventing awareness or prevent surgical complication due to fast emergence or to enhance operation room efficiency?
Thank you for your question.
Sleep disorders are common in the clinic and have received extensive attention in recent years. Animal studies have shown that rats with sleep deprivation alter the sensitivity to the anesthetics. The purpose of the study was to observe whether the concentration of inhaled anesthetics in patient with sleep disturbances is different from those with normal sleep habits in clinical anesthesia, thus may guide clinical medication in the future.

2. Did the anesthesiology well know the score of PSQI, HAMA, and HAMD?
Thank you for your question.
Usually, the anesthesiologists do not understand these scales very well.
But, the first author participated in a national psychological counseling course conducted by psychiatrists and psychologists before the study, which including a detailed introduction and assessment guidance for the sleep, anxiety, and depression scales. She passed the exam at last and obtained secondary psychological consultant certification. The picture of certificate was proved in the cover letter.
3. Did all patients meet the scales?
   Thank you for your question.
   Yes, all the patients meet the scales.

4. Did all patient hold (no eat) the sleeping medicine before the day of surgery? It might affect the awake concentration of sevoflurane and orexin-A.
   Thank you for calling this to our attention.
   All patients received no relevant medication before the observation, which has been described in the article. Page 5 Line 95-100: “Patients were excluded if they presented with any of these criteria: …… history of drug dependence or use of over-the-counter sleep medications within the previous 6 months.” Page 9 Line 161-163: “Five were excluded from the observation (2 did not give consent, 1 was obese, 1 had severe anemia, and 1 was using midazolam before observation) and one patient was excluded from the analysis for wracking cough during the observation.”

5. Why you represent “Glucose and liquid volume”? Did the two parameters affect the orexin-A?
   Thank you for your question.
   The liquid volume is represented because it may affect the concentration of sevoflurane, and glucose is one of the factors regulating the secretion of orexin.

6. The quality of figures is poor.
   Thank you for your comments.
   We've improved the quality of the figures.

H Dong (Reviewer 2): In this study, the authors investigated MACawake of sevoflurane in breast surgical patients with chronic sleep disorders. As the number of sleep patient is increasing, this study is of good clinical importance. The clinical trial was well designed. However, a few concerns need to be addressed.

1. This study was conducted in mid-aged female patients only, thus the conclusion cannot be spread into the whole patient entity. The enrolled patients were of 40-60, many of them may be experiencing menopausal symptoms which comprise of sleep disorders. Therefore, the menopausal condition should be considered in the study.
   Many thanks for your constructive comments. Indeed, the conclusion cannot be spread into the whole patient entity, so the relevant content about the conclusion in the manuscript has been modified.
   In the current study, sleep disorders are only distinguished by the PSQI scale, which only provide a comprehensive assessment. Thus, the causes and types of sleep disorders were not classified and detailed, and the menopausal condition in female patients of 40-60years old will be evaluated in future studies. We describe as the limitation in the paper (Page 12, Line 219-222).

2. Transient sleep disorders are very common in perioperative period; a number of patients don't sleep well in the hospital. Did the current study analyze the sleep status of the nights before surgery?
   Thank you for your question.
   The PSQI scale was used to evaluate the quality of sleep in the past one month. The evaluation was performed on the day before surgery, and therefore the results included the sleep conditions both at
home and after admission before surgery, but we did not distinguish them, and we did not analyze the sleep status of the nights before surgery (Page 6, Line 107-109).

3. How were the verb commands administered? What was the content?
Thank you for your question.
Verbal commands were given to test awakening by an independent observer who was blinded to the design and the aim of the study. The observer asked the patient to open eyes with a normal tone and repeated 3 times. If the patient responded correctly, that represented the patient is awareness, otherwise the patient is unconsciousness. The supplement of details has been modified in the article by highlighting (Page 7, Line 125-126).

4. Orexin decreases dynamically under general anesthesia, and increases after anesthesia. When was the plasma orexin-A tested? Was it a baseline level? Or, was it examined during anesthesia?
Indeed, the concentration of orexin-A varies according to the status of anesthesia, and thank you for your comments.
The plasma orexin-A was measured before the observation when the patient was awake, so it is a baseline level, which has been described in the article. Page 8, Line 139-140: “Blood samples (5 mL) were collected into EDTA tubes before observation for blood gas analysis and then transferred into centrifuge tubes containing aprotinin.”
However, we did not repeat the measurement of orexin-A considering that the whole observation of the study is fairly short. It would take few minutes for the patients to lose or recover the consciousness. We are planning to evaluate the variation of orexin-A in the following study.

5. Logistic regression curve should be graphed for the correlation of awakening concentration of sevoflurane and orexin-A level.
Thank you for your suggestion.
Probit analysis is also a kind of regression analysis, and has already graphed in the original text.

6. In Figure 3, the labels of two groups are missing.
Sorry for the negligence. We have added the labels, thank you for your comments.
Zhengyuan Xia (Reviewer 3): General comments: In this clinical study, the authors addressed an interesting topic and concluded that the MACawake of sevoflurane is higher in patients with sleep disorders compared to those with normal sleep habits. The increased anesthetic requirement may be related to changes of orexin-A levels. These findings, thus, suggest that sleep disorders may have a potential impact on clinical anesthesia, including changes of sensitivity to anesthetics or postoperative complications. The conclusion is overall supported by data. This reviewer has the following concern/suggestion the authors need to address:

Specific comments:

1. The duration of surgery in each group is not clear, which need to be provided.
Thank you for your suggestion.
The end point of the study was before the induction of anesthesia, which means all the data were
recorded before the surgery. After the observation, the general anesthesia was then carried on to perform the surgery. Therefore, the parameters of the surgery were not recorded.

2. While the authors described the way why and how the sevoflurane concentration was adjusted, however, the use (dosage) of opioid or other major sedatives was not provided which may affect the concentration of sevoflurane needed. Thank you for your comments.

   The primary aim of the current study was to observe the MACawake of sevoflurane, and all the tests were carried out before the induction, so we did not use any drugs that might affect the concentration of sevoflurane, such as opioids, other sedatives, and so on.

3. English writing may need to be polished by a Native English speaker or by a professional medical English editing service (e.g., www.iwdwbio.com)

   We’ve polished the writing before the submission by a professional medical English editing service. Thank you for your recommendation.