Dear Dr. Jin-Lei Wang,

Thank you very much for your decision letter and advice on our manuscript entitled. “Effect of anesthesia induction with butorphanol on postoperative nausea and vomiting: A randomized controlled trial”. We also thank the reviewer for the constructive comments and suggestions. We have revised the manuscript accordingly, and all amendments were indicated in red font in the revised manuscript. In addition, the point-by-point responses to the comments are listed below this letter.

This revised manuscript has been edited and proofread by Medjaden Inc.

We hope that the revised manuscript would be acceptable for publication in your journal, and we look forward to hearing from you soon.

Yours sincerely,

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First of all, we would like to express our sincerest gratitude to the reviewer for the constructive and positive comments.

Replies to Reviewer 1

Thank you for taking the time to review our article. We appreciate your valuable feedback and have addressed each of your comments accordingly. Please find our responses below:

Specific Comments

1. The manuscript is important; however, it needs amendments. Abstract: Methods: I would recommend that "prospective, double-blind" be inserted before the study.

Response: The term "prospective, double-blind" was included before the study, as recommended by the reviewer.

2. Results: I would recommend you mention postoperative nausea/vomiting first followed by doses of anesthetics and hemodynamics, because your primary focus was postoperative nausea/vomiting.

Response: The content was rearranged to mention postoperative nausea/vomiting first, followed by doses of anesthetics and hemodynamics, in order to better reflect the primary focus of the study.

3. Conclusion: I would recommend you state your conclusion in the past tense. This study reveal[ed] that butorphanol [was]…and improv[ed] the comfort of patients...

Response: We thank the reviewer for the thoughtful suggestion. The conclusion was modified to be in the past tense, stating that the study revealed the efficacy of butorphanol in improving patient comfort.

4. Core Tip: I would recommend the expression "and it was found that" be deleted. I would recommend the sentence of "The BCS… in the PACU." be changed to "The patients in the butorphanol group were more comfortable than those in the sufentanil group in the PACU."

Response: The expression "and it was found that" was removed, as suggested by the reviewer. In addition, the sentence on patient comfort in the PACU was modified to state that patients in the butorphanol group were more comfortable than those in the

sufentanil group.

5. Introduction: As your study was clinical one, you should focus more on the clinical studies of butorphanol and sufentanil on postoperative nausea/vomiting, rather than basic mechanisms of nausea/vomiting and analgesia via opioid receptors. Most of your introduction should be moved to discussion section. The sentence "In addition, butorphanol… endotracheal intubation.[11] be deleted or moved to discussion section.

Response: We thank the reviewer for the insightful suggestion. We understand the reviewer's concern on the emphasis on the basic mechanisms of nausea/vomiting and analgesia *via* opioid receptors in the Introduction section of the study. Since this is a clinical study, it can be agreed that it is vital to prioritize clinical aspects. In order to address this issue, the content related to basic mechanisms was significantly reduced in the Introduction section. Furthermore, the Discussion section was expanded to provide a more comprehensive analysis of clinical studies that involved butorphanol and sufentanil, and its impact on postoperative nausea/vomiting.

The reviewer noted that the sentence, "In addition, butorphanol...endotracheal intubation.[11]," should either be deleted or moved to the Discussion section. We concur with the suggestion of the reviewer. We decided to entirely remove this sentence from the Introduction section.

6. I would recommend "Material and Methods" be changed to "[Patients] and Methods."

Response: The heading was changed to "Patients and Methods", as suggested by the reviewer.

7. Page 6, paragraph 1: "Anesthesia induction was…analgesic titer ratio." should be moved to "Anesthesia Method" section. Page 6, paragraph 2: Your manuscript says that "Based on previous studies and preliminary experiments [12, 13], the sample size…PONV." I presume this would indicate you did preliminary study of butorphanol on postoperative nausea/vomiting. However, the references did not include your studies. If you did preliminary experiments, you should cite your manuscript(s). I think the manuscript by Fujii and Itakura (Ref. 13) has been retracted. I do not think you can cite Ref 13.

Response: Information on the anesthesia induction and analgesic titer ratio was moved to the "Anesthesia Method" section.

We apologize for the confusion caused by the lack of citation for the preliminary studies. Indeed, the overall sample size was calculated based on the existing literature and the preliminary pilot experiments. The findings from the initial pilot experiments have not been published, to date. The citation for Ref. 13 was removed, since this has been retracted. We would like to extend our sincerest apologies for inadvertently inputting 45% on the keyboard, instead of the intended 35%. The corresponding text was modified in the revised manuscript, as follows: “Based on the preliminary experiments and previous studies, the sample size was calculated according to the incidence of PONV. The preliminary experiment results indicated that the incidence of PONV was approximately 35% in the sufentanil group, and 13% in the butorphanol group. In order to ensure adequate statistical power with 85% power at 5% level of significance, at least 49 patients were required for each group. Accounting for the potential 10% dropout rate, a total of 110 patients were included for the present study.”.

8. Page 7: You measured blood pressure by non-invasive method. You also measured arterial blood pressure with radial artery cannulation and you cannulated the internal jugular vein. Were these your routine monitoring methods even for patients who underwent just laparoscopic gastrointestinal surgery?

Response: Elderly individuals may have multiple comorbidities, and have a higher risk of cardiovascular complications during surgery. Continuous blood pressure monitoring assists in promptly detecting any hemodynamic changes, allowing for timely intervention, when necessary. In addition, accurate blood pressure monitoring is crucial when administering anesthesia, and adjusting the patient’s fluid status during the procedure. Therefore, the routine use of invasive blood pressure monitoring in elderly patients undergoing gastrointestinal laparoscopic surgery was generally considered. The arterial line provides real-time information on the systemic blood pressure, while the central venous catheterization allows for the monitoring of central venous pressure, and facilitates the administration of fluids and medications. Therefore, the corresponding text was modified in the revised manuscript, as follows: “Invasive arterial blood pressure was also monitored *via* radial artery catheterization, and by internal jugular vein catheterization, in order to detect any hemodynamic changes, and facilitate the administration of fluids and medications, when necessary.”

9. As you compared the doses of propofol and remifentanil between the groups, you need to state how you titrated the doses of propofol and remifentanil during the surgery.

Response: Propofol and remifentanil were administered by micropump infusion. The cumulative dose of propofol and remifentanil administered during the surgical procedure was determined using a micropump infusion device. During the induction phase of anesthesia, propofol was intravenously administered at a dose of 1-2 mg/kg using a micropump infusion device. Concurrently, remifentanil was infused at a rate of 5-10 μg/kg/h. During the maintenance phase of anesthesia, propofol was intravenously administered at a rate of 4-6 mg/kg/h, while remifentanil was infused at a rate of 5-10 μg/kg/h. In order to calculate the total dose of propofol and remifentanil administered during the surgery, the infusion rates of the anesthetic drugs, the patient's weight, and the duration of the surgical procedure, as documented in the anesthesia record, were considered. The following formula was used: dose = infusion rate (mg/kg/min or μg/kg/min) × patient weight (kg) × duration of surgery (min). The sum of the amounts given during both the induction and maintenance stages of anesthesia would yield the total administered dose. In addition, it was clarified how the doses of propofol and remifentanil were titrated during the surgery.

10.Results: You only stated that the patients received laparoscopic gastrointestinal surgery. I think gastrointestinal surgery includes various procedures. More detailed statements of gastrointestinal surgery would be preferable. Continuous variables other than operation time should be rounded off to one decimal place.

Response: We thank the reviewer for the insightful suggestion, The study merely investigated the operation of gastrointestinal tumors. The specific operation names were not collected and analyzed for the time being, which was the shortcoming of the experiment.

We thank the reviewer for the insightful suggestion. The study aimed to investigate various aspects related to laparoscopic gastrointestinal tumor surgery, including patient demographics, surgical outcomes, and postoperative complications. However, a dedicated statistical analysis of the specific surgical techniques employed during the operations was not performed. Thus, this limitation was acknowledged in the Discussion section of the manuscript. As stated in the limitations section, the focus was primarily on exploring the complications associated with butorphanol or

sufentanil after laparoscopic gastrointestinal tumor surgery. Although the importance of analyzing specific surgical techniques was acknowledged, the study design did not allow for an in-depth statistical analysis in this regard. We understand that this limitation may affect the comprehensiveness of the research. We appreciate the feedback of the reviewer, and we agree that future studies should include a robust statistical analysis of the specific surgical details for a more comprehensive assessment.

11. Table 3 What is “windpipe?” Medical term of “windpipe” is preferable.

Response: The term “windpipe” was replaced with the preferred medical term.

12. Page 9, paragraph 2: I think the incidences of nausea/vomiting are most important in your study. More detailed statement is essential. It would be more understandable if you would include the actual doses of propofol and remifentanil, incidences of agitation, BCS scores, and effective compressions of PCIA in table.

Response: More detailed statements on the incidence of nausea/vomiting were included, as suggested by the reviewer. In addition, the actual doses of propofol and remifentanil, incidences of agitation, BCS scores, and effective compressions of PCIA were included in Table 5 for improved clarity.

13. Discussion: I would recommend that you concisely summarize your most important findings in the first paragraph. As your study was clinical one, I would recommend you discuss more on clinical effects of butorphanol and sufentanil on postoperative nausea/vomiting than basic discussions on butorphanol and sufentanil. That would improve the clinical values of your excellent study.

Response: We thank the reviewer for the insightful suggestion. The Discussion section was modified, accordingly.

14. Conclusion: I think conclusions should be stated in the past tense, not in the present tense.

Response: The Conclusion section was modified to be stated in the past tense, as recommended by the reviewer.

Once again, we appreciate the thorough review and guidance of the reviewer, which improved the quality of the manuscript. We hope that the amendments would be able to address all concerns, and enhance the clarity and relevance of the study.

Thank you for considering the revised manuscript.