December 11, 2022

Editorial Office
World Journal of Clinical Cases
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Re: Revision of Manuscript (NO.: 80712, Clinical Trials Study)

Dear Editors,

We are pleased to receive the preliminary decision that our manuscript entitled, "*Efficacy and safety of propofol target-controlled infusion combined with butorphanol for sedated colonoscopy,*" is acceptable for publication pending appropriate revision. Thank you very much for the favorable decision and positive review of the manuscript. The valuable comments and suggestions have helped to improve the quality of the manuscript.

Accordingly, we have modified the manuscript, with all changes highlighted in red in the revised manuscript. In addition, all issues were addressed in the point-by-point responses below this letter.

This revised manuscript was edited and proofread by an academic editor of *Medjaden* Inc.

We believe that the manuscript has significantly improved, and hope that the revised manuscript would be acceptable for publication in the *World Journal of Clinical Cases.*

As always, we are grateful for your interest in our study, and we look forward to hearing from you.

Yours sincerely,

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Point-by-Point Responses:

Replies to Reviewer #1

Reviewer #1:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (High priority)

Response: We sincerely appreciate the reviewer's recognition of the strengths of our work. With regard to the concerns, these issues were addressed in the revised manuscript, and in the point-by-point responses below.

Specific Comments to Authors:

1. This is pretty good research, it introduce an important development in GIT practice by using butorphanol as adjunct to Propofol in sedating patients during colonoscopy. However, what informed the choice of butorphanol and leave the readily available opioids?

Response: We thank the reviewer for the comment. In this study, butorphanol was selected as an adjunct to propofol in sedating patients during colonoscopy. Butorphanol, a synthetic opioid, has higher affinity for opioid receptors than opioids, Compared to morphine, butorphanol is three times more potent, and has a shorter duration of action (range, 0.5-3.0 hours). In addition, butorphanol has lower respiratory depression than morphine, low toxicity, and low potential for abuse. In light of the reviewer's comment, the above information was added to the Introduction section of the revised manuscript.

References

Agarwal A, Raza M, Dhiraaj S, Pandey R, Gupta D, Pandey CK, Singh PK, Singh U. Pain during injection of propofol: the effect of prior administration of butorphanol. *Anesth Analg* 2004; 99: 117-119. [PMID: 15281515 DOI: 10.1213/01.ane.0000117002.03919.49]

Zhu X, Chen L, Zheng S, Pan L. Comparison of ED95 of Butorphanol and Sufentanil for gastrointestinal endoscopy sedation: a randomized controlled trial. *BMC Anesthesiol* 2020; 20: 101. [PMID: 32359348 DOI: 10.1186/s12871-020-01027-5]

2. The use of high dose butorphanol was proven to reduce the total dose of propofol used in colonoscopic sedation and hence reduce the possible adverse events. However, was there a follow up to ascertain presence of possible side effects regarding the high dose butorphanol?

Response: We thank the reviewer for recognition of the strength of our work. With respect to the reviewer's question, the common side effects of butorphanol were explained to the patients, but a follow-up visit was not scheduled to ascertain the possible side effects of the high-dose butorphanol after colonoscopy. According to the expert consensus on butorphanol tartrate analgesia in China (Huang *et al.*, 2011), the most commonly reported side effects of high-dose butorphanol include drowsiness and dizziness, which do not need any further medical treatment.

Reference

Huang Y, et al., Expert consensus on butorphanol tartrate analgesia. Journal of Clinical Anesthesiology (Chinese) 2011, 27 (10): 1028-1029.

3. Though butorphanol was found to reduce dosage of propofol used during colonoscopy, it was not able to assess the possible compounders as pre-procedural psychological state as well as depth of sedation achieved during the procedure.

Response: We thank the reviewer for the careful review. We agree that despite this finding, the possible compounders in the pre-procedural psychological state and the depth of sedation achieved during the procedure were not assessed. It was considered that this may go beyond the scope of the clinical trial in evaluating the efficacy and safety of propofol target-controlled infusion in combination with butorphanol for sedation during colonoscopy. However, we consider this worthy of further investigation, and we will consider this in our future studies.

Replies to Reviewer #2

Reviewer #2:

Scientific Quality: Grade D (Fair)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision

Response: We thank the reviewer for providing these valuable suggestions, which have been truly helpful in improving the manuscript. With respect to the concerns, the issues were addressed in the revised manuscript, and in the point-by-point responses.

Specific Comments to Authors:

Mention the evolution of intravenous anesthesia, models available today of of target-controlled infusion (TCI) and their benefits compared to other techniques that did not use pharmacokinetic models to help titrate the desired target. It was not discussed which pharmacokinetic model was used (pharmacokinetic variables and their discussion and correlation in clinical applicability). The time and volume that the butorphanol bolus will be administered were not mentioned explicitly and clearly. Presentation and classification of butorphanol is not described.

Response: We thank the reviewer for the careful review. The Introduction, Materials and Methods, and Discussion sections were revised. These are presented below for reference:

In the Introduction section, additional information on target-controlled infusion (TCI) and butorphanol were included, and were highlighted in red font.

"The results of previous studies suggest that propofol, particularly delivered by target-controlled infusion (TCI), which is a drug delivery technique to achieve the desired anesthetic drug concentration performed using a pharmacokinetic model and patient characteristics (*i.e.* age, gender and body mass index), is an effective anesthetic with rapid onset and short recovery.[11, 13-18] Compared to conventional methods of administrating drugs during anesthesia, such as bolus injection with a syringe and continuous infusion with an infusion pump, TCI provides a relatively constant concentration at the target site, and a more rapid recovery time. "

"For instance, butorphanol, which is a synthetic opioid, has higher affinity for opioid receptors, when compared to opioids. Compared to morphine, butorphanol has higher analgesic potency, a similar duration of action, and lower respiratory depression. Furthermore, butorphanol is a mixed opioid

agonist/antagonist, which includes an agonistic action on the kappa-opioid receptor and agonistic/antagonistic effects on the mu-opioid receptor. This exerts an analgesic effect mainly by agonizing the kappa-opioid receptor. In addition, butorphanol can be used to mitigate the respiratory depression of mu-opioid agonists. The advantages of butorphanol include low toxicity and low potential for abuse. Previous studies have revealed that in comparison with other synthetic opioid analgesic drugs (e.g. sufentanil), butorphanol has less anesthesia-related AEs, such as respiratory depression, decreased gastrointestinal activity and smooth muscle spasm, itchy skin, urinary retention, physical and physiological dependence, nausea, and vomiting. [25, 26]. Furthermore, butorphanol has been widely used in anesthesia for patients undergoing gastrointestinal endoscopy."

In the Materials and Methods section, additional information on the butorphanol used for the study were included, and denoted in red font.

"The Butorphanol Tartrate Injection (Trade Name, Nuoyang; 2 mL:4 mg; Batch no. h20143106) was manufactured by Jiangsu Hengrui Pharmaceutical Co., Ltd. (Nanjing, Jiangsu, China)."

"For the anesthesia, at 10 minutes before the colonoscopy, the patients intravenously received butorphanol at a dose of 5 μg/kg in Group B1 and 10 μg/kg in Group B2, and patients in Group C received NS."

In the Discussion section, the Marsh model was used as the pharmacokinetic model for the discussed propofol TCI.

"The TCI system can be programmed using any of the two main pharmacokinetic models: the Marsh model and Schnider model. The Marsh model has weight as a model parameter, while the Schnider model has

multiple parameters (*e.g.* age, weight, height, and lean body mass). Chen *et al.* examined the performance of the Marsh model and Schnider model for TCI propofol, and suggested that the Marsh model was overall superior to the Schnider model, and more suitable for TCI propofol. Therefore, for the study, the Marsh model was selected as the pharmacokinetic model to program the TCI system for propofol."

References

Lv S, Sun D, Li J, *et al*. Anesthetic effect of different doses of butorphanol in patients undergoing gastroscopy and colonoscopy. *BMC Surg 2021;* 21: 266.

Struys MM, De Smet T, Glen JI, et al. The History of Target-Controlled Infusion. Anesth Analg. 2016,122(1):56-69.

Mu JJ, Jiang T, Deng LP, et al. A comparison of two techniques for induction of anaesthesia with target-controlled infusion of propofol. Anaesthesia.2018 ,73(12):1507-1514.

Chen S, Lin W, Wang C, et al. Comparison of accuracy of the Marsh model and the Schnider model in target-controlled infusion of propofol. Chinese Journal of Anesthesiology, 2015, 35 (12): 1466-1469.

Limitations of using other opioids (mainly mu total agonists) when butorphanol is used are not described and developed in the text. Comparison of opioid types on page 6 could be further elaborated with the PK/PD correlation between the opioids cited (what is the intention of the comparison? one with sedative intent and the other with analgesic intent?

Response: We thank the reviewer for the careful review. In the study, butorphanol, rather than opioids, was used mainly due to its advantages. Butorphanol, which is a synthetic opioid, has higher affinity for opioid receptors, when compared to opioids, Compared to morphine, butorphanol is approximately three times more potent, with higher analgesic potency, and has a similar duration of action and lower respiratory depression. Furthermore, butorphanol is a mixed opioid agonist/antagonist, which includes an agonistic action on the kappa-opioid receptor and agonistic/antagonistic effects on the mu-opioid receptor. This exerts an analgesic effect mainly by agonizing the kappa-opioid receptor. Moreover, butorphanol can be used to mitigate the respiratory depression of mu-opioid agonists. The advantages of butorphanol include low toxicity and low potential for abuse. In light of the reviewer's comment, the relevant sentences were modified in the Introduction section of the revised manuscript. These are presented below for reference:

"For instance, butorphanol, which is a synthetic opioid, has higher affinity for opioid receptors, when compared to opioids. Compared to morphine, butorphanol has higher analgesic potency, a similar duration of action, and lower respiratory depression. Furthermore, butorphanol is a mixed opioid agonist/antagonist, which includes an agonistic action on the kappa-opioid receptor and agonistic/antagonistic effects on the mu-opioid receptor. This exerts an analgesic effect mainly by agonizing the kappa-opioid receptor. In addition, butorphanol can be used to mitigate the respiratory depression of mu-opioid agonists. The advantages of butorphanol include low toxicity and low potential for abuse."

References

Zhu X, Chen L, Zheng S, Pan L. Comparison of ED95 of Butorphanol and Sufentanil for gastrointestinal endoscopy sedation: a randomized controlled trial. *BMC Anesthesiol* 2020; 20: 101.

Lv S, Sun D, Li J, *et al.* Anesthetic effect of different doses of butorphanol in patients undergoing gastroscopy and colonoscopy. *BMC Surg 2021;* 21: 266.

Develop and make clear the reason for the comparison and have a clear conclusion about the correlation page 9 - awakening concentration of propofol - change to target plasma concentration of propofol (the plasma concentration of propofol was not measured) Be clear which test was used to check the distribution of the data (parametric or non-parametric). Example: Was the shapiro wilk test done? Figure 1 and 2 show with some kind of marker the groups that statistical difference occurred Develop in discussion the results presented in figures and tables. Develop into discussion the results presented in figures and tables.

Response: We thank the reviewer for the careful review. The original data was reviewed, and a further search was performed for this literature. No clear correlation between the awakening concentration of propofol and target plasma concentration of propofol was identified in the study. In addition, there are no reports on the correlation between the awakening concentration of propofol and target plasma concentration of propofol.

Correlate with other similar articles and discuss particularities, differences, etc. The title includes "Efficacy and safety of propofol", however, in the discussion it is not developed, and characterized and/or correlated with the words efficacy and safety. Poor discussion of the pharmacokinetic concepts of propofol (three-compartment, cosntants used in the pharmacokinetic model

used in the technique), develop synergism and pharmacokinetic interactions that occur in the use of opioids.

Response: We thank the reviewer for the comments. The Discussion section was modified, accordingly, in the revised manuscript. For the synergism and pharmacokinetic interaction that may occur with the use of propofol and butorphanol, this remains unclear, but is worthy of further investigation.

"The TCI system can be programmed using any of the two main pharmacokinetic models: the Marsh model and Schnider model. The Marsh model has weight as a model parameter, while the Schnider model has multiple parameters (*e.g.* age, weight, height, and lean body mass). Chen *et al.* examined the performance of the Marsh model and Schnider model for TCI propofol, and suggested that the Marsh model was overall superior to the Schnider model, and more suitable for TCI propofol. Therefore, in the study, the Marsh model was selected as the pharmacokinetic model to program the TCI system for propofol."

References

Struys MM, De Smet T, Glen JI, et al. The History of Target-Controlled Infusion. Anesth Analg. 2016,122(1):56-69.

Mu JJ, Jiang T, Deng LP, et al. A comparison of two techniques for induction of anaesthesia with target-controlled infusion of propofol. Anaesthesia.2018 ,73(12):1507-1514.

Chen S, Lin W, Wang C, et al. Comparison of accuracy of the Marsh model and the Schnider model in target-controlled infusion of propofol. Chinese Journal of Anesthesiology (Chinese), 2015, 35 (12): 1466-1469.

6 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

The manuscript has been peer-reviewed, and it' s ready for the first decision.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade C (Good)

Response: We thank the editor for the positive review of the manuscript.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Response: We are grateful to the editor for the favorable decision and positive review of the manuscript.

Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Response: As suggested by the editor, the original figures were provided, which were prepared and reprocessed using PowerPoint.

In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will

indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

Response: We thank the editor for the suggestion. Accordingly, the information "Copyright © The Author(s) 2022" was included in the bottom right-hand side of the image in the PowerPoint.

Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Response: We thank the editor for the careful review. All tables were checked, and the standard three-line table format was followed.

Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the RCA. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA

database for more information at: https://www.referencecitationanalysis.com/.

Response: We thank the editor for the suggestion. The new tool RCA was applied to obtain the search results in the revision of the manuscript. We greatly appreciate the helpful information, especially the artificial intelligence technology-based citation analysis databases.

As always, we are grateful for your interest in our study, and we hope that the revised manuscript would be acceptable for publication in the *World Journal of Clinical Cases*.