Author’s response to reviews

Title: Doxapram alleviates low SpO2 induced by the combination of propofol and fentanyl during painless gastrointestinal endoscopy

Authors:

Xin Lian (tomytomytomy123@sohu.com)
Xin Lian (tomytomytomy123@sohu.com)
Haoxing Wang (wanghaoxing2005@126.com)
Chunxiao Hu (18626311198@163.com)
Zhiping Wang (zhpsqxt@163.com)
Shunmei Lu (lushunmei2008@163.com)
Jingjing Xu (jingjing6104@126.com)
Yiling Qian (ylqian-1987@163.com)
Jun Wang (wangjun19710930@126.com)

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Reviewer’s response to reviews:

Reviewer reports:

Alessandro Belletti, M.D. (Reviewer 1): Dr. Xin Lian and colleagues have now submitted a revised version of their manuscript. Most of my comments have been adequately addressed; however, there are still some issues that require to be fixed by the Authors

1. The Authors have not replied to my comment on EtCo2 monitoring. Please comment in the manuscript whether EtCO2 monitoring was used or not

Response:
Thanks for this valuable suggestion. We described in the manuscript that ETCO2 monitoring hadn’t been used for lacking of function on our monitor in the paragraph of limitations in line 254-256.

2. Thanks for presenting data on doxapram adverse effects. However, please add these data in a table or within the Results section as well
Response:

Thanks for this valuable suggestion. We had added data of adverse effects of doxapram with increased heart rate within the Results section in line 172-173.

3. I still do not clearly understand how sample size was calculated. I do not understand why the Authors did not present in the manuscript the data they report in the Reply to my previous comment. Furthermore, it is still unclear to me which power they used in sample size calculation (90% or 75%).

Response:

Thanks for this valuable suggestion. As for the calculation of sample size, we consulted professors related to statistics and redescribed in the section with equation in line 106-114.

4. Please provide details in the Methods section regarding the methods for random sequence generation, as well as for allocation concealment. Please specify whether outcome assessor were blinded to study group assignment as well

Response:

Thanks for this valuable suggestion. We described the random allocation with computer and put in envelope in the Methods section in line 115-116. The outcome assessor were blinded to study group assignment in line 120-121.

5. Please provide a figure with the study flow-chart as per CONSORT recommendations

Response:

Thanks for this valuable suggestion. We provided a figure with the study flow-chart as per CONSORT recommendations. Please see the supplementary materials.

6. Please clearly define the primary outcome of the study in the Methods section

Response:

Thanks for this valuable suggestion. We clearly define the primary outcome of the study in the Methods section in line 135-136.

7. Please provide at least one reference for doxapram mechanism of action

Response:

Thanks for this valuable suggestion. We provide reference 16 for one of doxapram mechanisms of action in line 217-219.
The following sentence is not correct: "...ask for diagnostic painless gastrointestinal endoscopy; voluntary to participate the study with informed consent". I would rather suggest "scheduled for diagnostic gastrointestinal endoscopy; provision of written informed consent"

Response:

Thanks for this valuable suggestion. We modified "...ask for diagnostic painless gastrointestinal endoscopy; voluntary to participate the study with informed consent" into "scheduled for diagnostic gastrointestinal endoscopy; provision of written informed consent" in line 94-95.

Ya-Jung Cheng (Reviewer 2): Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format. Please overwrite this text when adding your comments to the authors. The authors have clearly stated their hypothesis. The idea of adding a respiratory stimulant with the common intravenous sedation to reduce the incidence of respiratory depression is very interesting. However, in two groups of 55 patients with wide age ranges, the comparable dosage of anesthetics did not indicate the comparable anesthetic depth which will deeply affect the respiratory depression. The major results of this study were confusing for firstly from records on the monitor (SPO2) but later from the responses to hypoxemia SPO2 < 90% by every 10 seconds. It is hard for readers to differentiate the time for hypoxemia is due to the drug effects or the inadequacy of effective ventilation. Furthermore, as the authors added in the manuscript line 212-216, what is the cost/benefit of adding doxapram on reducing 20% (from 8/55 to 19/55) of patients with a face mask or jaw lift?

The abstract and conclusion:

line 46, there were no statistical differences in oxygen saturation at "the following time points". conclusion: It would be precise with" We conclude that adding doxapram with intravenous propofol reduces the incidence of respiratory depression in the first three minutes during painless gastrointestinal endoscopy without affecting propofol....................." It is the result. Doxapram does not prevent all the respiratory depression. The conclusion in line 247 to 250 is correct. Based on the results, the title may be over elaborated.

table 1, I suggest to change to group D (n=55), group S (n=55), then the readers know the incidence.
table 2, S (n=55), D (n=55) ** remains wrongly stated. figure 1, *** is meaningless.

Response:

Thank Professor Ya-Jung Cheng for your kind and professional comments!

(1) Comparable dosage of anesthetics did not indicate the comparable anesthetic depth which may be affected by doxapram. We modified “In our study, the dose of propofol in both groups was similar demonstrating that doxapram doesn’t affect the need of propofol in anesthesia” in line 240-241. Doxapram not only affects anesthetic depth, which we hadn’t monitored for.
lacking of function of the monitor, but also affects respiration depression that we had found was more important. We discussed in the paragraph of limitations.

(2) The SPO2 is comparable at the first 3 min without comparability afterwards that was affected by respiratory treatment, but the responses were comparable to hypoxemia SPO2 < 90% by every 10 seconds during the study.

(3) The drugs of propofol injection combined with fentanyl effect both hypoxemia and inadequacy of effective ventilation.

(4) We modified the explanation “This may relate to the effect of respiratory stimulation of doxapram and its duration of action.” In line 213-214 that will explain the results of “adding doxapram on reducing 20% (from 8/55 to 19/55) of patients with a face mask or jaw lift”.

(5) We had changed the word of “prevents” in the title with “allieviates”.

(6) We had changed into group D (n=55), group S (n=55) and S (n=55), D (n=55) in table 1 and 2.

(7) We had corrected ** under table 2 and *** in figure 1.

Raiko Blondonnet (Reviewer 3): The authors have improved their manuscript in order to provide a better understanding and readability to the readers. They have also provided all the answers to my interrogations.

Nevertheless, I have few concerns about the manuscript.

1. I think the authors should carefully proofread (again) the manuscript. Thus, there are still several typing mistakes (space missing between the words, the numbers, …) in both the abstract and the manuscript (+ figures). Please improve it.

Response:

Thanks for this valuable suggestion. We carefully read again the manuscript and modified several typing mistakes (space missing between the words, the numbers) in both the abstract and the manuscript.

2. I thank the authors to have answered to my interrogations about the limits in the revised manuscript but i think they should include all the limits in a single paragraph rather in each section of the discussion.

Response:

Thanks for this valuable suggestion. We collected all the limits in a single paragraph rather in each section of the discussion.

3. I don't understand the statistics. Indeed the authors wrote that the sample of the study was calculated using a power of 90% but in the next sentence they told us that they used a power of 75% for the primary outcome. Could the authors explain it?
Response:

Thanks for this valuable suggestion. We had redescribed the sample size calculation as commented by Professor Alessandro Belletti (Reviewer 1). We consulted professors related to statistics and carefully redescribed in the section with equation in line 104-112.

4. Even if the author have improved the readability of the figure 1, the authors should write if the bars are equivalent to standard-deviation error bars or SEM error bars.

Response:

Thanks for this valuable suggestion. We had rewritten the bars with standard-deviation error.