Author’s response to reviews

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

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Author’s response to reviews:

Although some modifications asked by the reviewers were made in the manuscript, the corresponding changes have not been made in the abstract. Please change "respiratory depression" (page 2, lines 38-39) for "low SpO2". In addition, remove the sentence "Respiratory depression, oxygen inhalation with a face mask and jaw lifting were all statistically different (P=0.0011, P=0.0148, P=0.0023, respectively)." and provide the P values at the end of the sentences just above, limiting the number at 3 decimals, for instance: "In group S, 26 patients experienced low SpO2 versus 10 in group D (p=0.001). In group S, 19 patients received oxygen inhalation with a face mask compared to 8 in group D (p=0.015). etc..."

Response: Thank you for your kind suggestions! We changed "respiratory depression" (page 2, lines 36-37) for "low SpO2". We removed "Respiratory depression, oxygen inhalation with a face mask and jaw lifting were all statistically different (P=0.0011, P=0.0148, P=0.0023, respectively)." and provided the P values at the end of the sentences just above, limiting the number at 3 decimals (page 2, lines 37-42).

- Page 3, lines 47-48: "There were no statistical differences in MAP and HR (except 1 min) between the two groups" is not clear enough. Maybe replace for "(except at the 1 min timepoint)" or "(except at 1 min after the induction)".
Response: Thank you for your precise suggestions! We changed (except 1 min) for "(except for the time point at 1 min after the induction)" (page 3, lines 44-45).

- page 3, line 51: "affecting" instead of "effecting"

Response: We modified "affecting" instead of "effecting" (page 3, line 48).

- background: applied in “Grade III, Level A” hospitals in China. What is a "Grade III, Level A hospital" ?? Please specify in order to make it clearer for non chinese readers
Response: We modified “Grade III, Level A hospital” for “Class-A Tertiary Hospitals” (page 4, lines 53-54)

- background: "Propofol, combined with analgesic, is the most common anesthetic method used for these procedures" : are you sure that combining propofol + opioids is the "most common anesthetic method for gastroscopy ? If so, provide a reference. Although rephrase for "Propofol, combined with analgesic, is commonly used for these procedures".
Response: We rephrased "Propofol, combined with analgesic, is the most common anesthetic method used for these procedures" for "Propofol, combined with analgesic, is commonly used for these procedures" and provided 3 references (page 4, lines 57-58).

- background: lines 67-71: please provide references for the mode of action of doxapram
Response: We provided references (page 4, line 67-70).

- background: lines 76-77: remove "Propofol consumption, heart rate (HR), and mean arterial pressure (MAP) were also measured" ; lines 77-78: remove "is unique in that it" from "Our study is unique in that it specifically compares, prospectively, the use of propofol/fentanyl..." > "Our study specifically compares, prospectively, the use of propofol/fentanyl..."
Response: We removed "Propofol consumption, heart rate (HR), and mean arterial pressure (MAP) were also measured" and "is unique in that it" (page 5, line 75-77).

- methods, lines 92-95: modify the sentence "The inclusion criteria included all patients > 18 years old, no gender limitation; no obvious diseases of heart, lung, liver, brain and kidney; no morbid obesity; scheduled for diagnostic gastrointestinal endoscopy with provision of written informed consent" for "All patients > 18 years old scheduled for a diagnostic gastrointestinal endoscopy were included in this study, since they consent to participate and sign the informed consent." and remove the rest of the sentence, as it is detailed just after.
Response: We modified "The inclusion criteria included all patients > 18 years old, no gender limitation; no obvious diseases of heart, lung, liver, brain and kidney; no morbid obesity; scheduled for diagnostic gastrointestinal endoscopy with provision of written informed consent" for "All patients > 18 years old scheduled for a diagnostic gastrointestinal endoscopy were included in this study, after submission of written informed consent." (page 5, lines 89-90).

- modify: "electrocardiography" for "electrocardiogram"
Response: We modified "electrocardiography" for "electrocardiogram" (page 5, line 94)

- modify the paragraph: For calculating the group size required to give an adequately small Type II error (i.e. adequate statistical power) we referred to the published studies about sufentanil anesthesia[1-3]. We calculated the sample size according to the equation as $n = \frac{Z_{\alpha/2}^2 \pi c (1-\pi c) (Q1-1+Q2-1)+Z_{\beta}^2 \pi 1 (1-\pi 1) Q1+\pi 2 (1-\pi 2) Q2 \pi 1-\pi 2}{2}$. Among the equation, $\alpha$ is the probability of type I error and we choose 0.05; $\beta$ is the probability of type II error and we choose 0.1; $\pi 1$ is the remission rate of respiratory depression in control group in our preliminary study and it is 50%; $\pi 2$ is the remission rate in observation group and it is 80%. We used 1 as a ratio of sample size (group 1/group 2) and statistical analysis of Chi-squared test. We got the number of cases with 52 required in each group. Finally, we choose 55 cases in each group of our study allowing a possible dropout of 5%." for "sample size calculation was made using a probability of type I error ($\alpha$) at 0.05, a power (1-$\beta$) of 0.90, a respiratory depression rate frequency of 80% and 50% in the control and intervention groups, respectively. Thus, 52 patients were required in each group. Considering that 5% of patient may be lost to follow-up, we included 55 patients in each group."
Response: We modified the paragraph according to your suggestions and agreed with you absolutely (page 6, lines 100-104).

- page 7, line 130: "nasal probes" instead of "nasal catheter" ?
Response: We modified "nasal tubes" instead of "nasal catheter". (page 7, line 120).

- page 7, line 135: modify "The primary outcome of the study is to investigate the effects of doxapram on alleviating respiratory depression" for "The primary outcome of the study is to investigate the effects of doxapram on respiratory depression" which is more accurate; "alleviating respiratory depression" being a result an I hope, not an outcome defined a priori.
Response: We modified "The primary outcome of the study is to investigate the effects of doxapram on alleviating low SpO2" for "The primary aim of the study is to investigate the effects of doxapram on low SpO2" (page 7, lines 124-125)

- results: modify "In total, 110 patients were enrolled in this study, included men and women, with ASAI-II." for "In total, 110 ASSA I-II patients were enrolled in this study".
Response: We modified "A total of 110 patients rated as ASA I-II were enrolled in this study (page 8, line 151).

- page 8, line 163: modify "including" for "regarding"
Response: We modified "with respect to" for "including" (page 8, line 153).

- results: limit the P values at 3 decimal places after the dot : "(P<0.001, P=0.007, and P=0.020)". And so on in the whole manuscript, tables and figures.
Response: We limited the P values at 3 decimal places after the dot in the whole manuscript.
- page 9, line 174: following the reviewers' comments change "Patients in group S had a higher incidence of respiratory depression" for "higher incidence of low SpO2". And so on in the whole manuscript.

Response: We changed “respiratory depression” for “low SpO2” and higher incidence of low SpO2 for higher incidence of respiratory depression, and in the whole manuscript. (page 8, line 164).

- discussion, lines 204-208: please provide references for these assertions about the Doxapram

Response: We provided references (17-19) for assertions about Doxapram (page 10, lines 196-198).

- line 209, modify "increased" for "higher" (SpO2 values)

Response: We modified "increased" for "higher" (page 10, line 199).

- lines 230-232: this sentence must absolutely be rephrased more cautiously. Your sample is obviously too small to conclude on the incidence off Doxapram side effects!! I suggest a sentence like: "We hadn’t found arrhythmia, dyspnea and hypertension in this study, although our sample is probably too small to conclude on Doxapram risk-benefit balance. Consequently, larger studies are required in order to conclude on the definite place of Doxapram during general anesthesia for gastrointestinal endoscopy."

Response: We rephrased the sentence for "Notwithstanding the absence of adverse effects as arrhythmia, dyspnea and hypertension in this study, our small sample size did not suffice to reach a compelling conclusion for a risk-benefit balance of doxapram." (page 11, lines 222-224). You suggestion is appropriate.

- lines 240-241: "Doxapram is often used to wake up patients after volatile anesthesia, such as sevoflurane[19]." I do not agree with this sentence. Doxapram is not "oftten" used for this purpose. In addition, the reference is irrelevant (an old study published in 1999 delaing with the mode of action of inhlated anesthetics). Modify absolutely.

Response: We agreed with your viewpoint and changed “often” for “occasionally”. In addition, we changed the reference for “reference 19”. (page 12, lines 234-235) as advised.

- lines 241-242: you could not write "In our study, the dose of propofol in both groups was similar demonstrating that doxapram doesn’t affect the need of propofol in anesthesia" as the depth of anesthesia was not monitored!! Rephrase more cautiously, or remove.

Response: We removed the sentence (page 12, line 242).

- lines 248-251: the sentence must be rephrased as the interpretation is wrong. The fact that "satisfaction of the endoscopist and patients was not different between the two groups did not demonstrate that anesthesia facilitates gastrointestinal endoscopy examination". Only a control
group without anesthesia would have demonstrate such a result. However, you could remove this sentence as it is now a well established fact, to which your study does not had new data.

Response: We removed the sentence (page 12, line 242) according to the viewpoint of respectable editor.

- lines 252-253: rephrase "It may be more precise if propofol is used under the guide of anesthetic depth such as bispectral index" to "results would have been more accurate if propofol had been delivered guided by the monitoring of anesthetic depth, as with a bispectral index for instance"

Response: Thank you for the kind advice, respectable editor! We rephrased the sentence (page 12, lines 242-244).

- lines 262-263: modify "Doxapram could decrease the recovery time in PACU should be payed attention and compared" for "Whether doxapram could decreased the recovery time in PACU in this setting should be investigated in further studies".

Response: Thank you for kind guide, respectable editor! We modified "Nonetheless, with respect to the care of outpatients, early safe discharge from PACU is of importance for the improved medical efficiency and the medical care system at large, thus awaiting more profound investigations as to whether doxapram could decrease the emergence time in scenario of PACU. (page 12-13, lines 251-255).

- Conclusion: as in the whole manuscript change "respiratory depression" by "decreased SpO2"

Response: Thank you for kind advice, respectable editor! We change "respiratory depression" by "low SpO2" in the whole manuscript as suggested by the reviewer’s previous suggestion, because low SpO2 means less than 90% that is defined in our manuscript (line 125). If the SpO2 decreased from 99% to 90%, it can also be considered decreased SpO2.