Author’s response to reviews

Title: Doxapram alleviates low S p O2 induced by the combination of propofol and fentanyl during painless gastrointestinal endoscopy

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Author’s response to reviews:

Alessandro Belletti, M.D. (Reviewer 1): Dr. Xin and colleagues present in this manuscript results of randomized placebo-controlled trial evaluating the effect of doxapram in reducing the incidence of respiratory depression during gastrointestinal endoscopy under sedation with propofol. They found that patients randomized to doxapram group had a lower incidence of respiratory depression (defined as need for supplemental oxygen) and need for airway rescue manoeuvres, without affecting depth of sedation or quality of examination.

I believe this is an interesting study, given the worldwide volume of minor procedures under deep sedation outside the safe environment of an operating theatre, frequently without assistance from a trained anesthesiologist.
My major comment on this manuscript is lacking of an end-tidal CO2 monitoring. This is now considered part of standard anesthesia monitoring by many professional societies. Did the Authors measured also etCO2 in their patients?

Additional comments:

1. Please provide a description of inclusion criteria as well, in addition to exclusion criteria.

Response:

Thanks for this valuable suggestion. We have added descriptions of inclusion criteria before exclusion criteria in line 85-88.

2. As a related point, please move details on enrolled patients (age range and ASA class) to the Results section, as well as the total number of patients randomized. As a general rule, please leave only general description of the methods in the Methods section, and leave description of enrolled patients characteristics in the Results section.

Response:

Thanks for this valuable suggestion. We have moved the details on enrolled patients (age range and ASA class) to the Results section, as well as the total number of patients in line 145-147.

3. I appreciate details on sample size calculation; yet they are quite unclear. Please provide a clear description of expected incidence of respiratory depression in the control group, as well as the expected reduction in the doxapram group.

Response:

Thanks for this valuable suggestion. We expected incidence of respiratory depression in the control group exceed 50% and expected reduction 10% in the doxapram group.

4. Please report full p-values rather tha p<0.05 in both abstract and main text.

Response:

Thanks for this valuable suggestion. We have reported full p-values in both abstract and main text.
5. Please add a very short description (1, max 2 sentences) of doxapram mechanism of action also in the Introduction.

Response:

Thanks for this valuable suggestion. Add 2 sentences of description about doxapram mechanism of action in the Introduction in line 67-70.

6. Which are doxapram side effects?? please describe the most relevant and the most severe side effects and report their incidence

Response:

Thanks for this valuable suggestion. We had described the side effects of doxapram including the most relevant and the most severe ones followed reporting incidence in the section of discussion in line 210-215.

Ya-Jung Cheng (Reviewer 2): Doxapram prevents respiratory depression induced by the combination of propofol and fentanyl during painless gastrointestinal endoscopy

Major concerns

1. Please clarify the definition of respiratory depression. The respiratory depression was defined by SpO2 < 90% at first. Then the authors described the following management: facemask after 10 seconds' desaturation (SpO2< 90%), jaw lifting after 10 seconds facemask with desaturation, assisted ventilation after 10 seconds jaw lifting with desaturation (SpO2< 90%).

Response:

Thanks for this valuable suggestion. We clarify the definition of respiratory depression with reference in line 125. We mean to use facemask to treat respiratory depression when SpO2< 90%. Further management as jaw lifting will be used if SpO2 still less than 90% with facemask use for 10 seconds. Assisted ventilation would be applied after 10 seconds jaw lifting with desaturation (SpO2< 90%).
2. As shown as above, in table 2, the incidence of desaturation was significantly lower in D group, but lasted less than 30 seconds. The need of assisted ventilation was low (2-4/55 patients) and comparable between two groups.

Response:

Thanks for this valuable suggestion. The incidence of desaturation lasted less than 30 seconds in table 2. Because we could not insure the SpO2 wouldn’t decrease in the following time that may lead hypoxia and dangerous the patients. We observed that the need of assisted ventilation was low (2-4/55) and there was no difference. We mistakenly lost the word “no” before the word “difference” in the note under table 2 for P= 0. 4011.

3. As shown in figure 1, the SPO2 was significantly higher within the first 3 minutes. Heart rate was significantly higher at the first minute.

Response:

Thanks for this valuable suggestion. As shown in figure 1, the SpO2 was significantly higher in group D than that in group S within the first 3 minutes. This may relate to the effect of respiratory stimulation of doxapram and its duration of action. We discussed in line 200-201. Heart rate was significantly higher at the first minute. It may relate to the side effect of heart rate increasing by doxapram which is good to prevent bradycardia caused by propofol. We discussed it in line 224-227.

4. What is the clinical impact for injection doxapram with induction agents? It is possible for patients to have respiratory depression and all the anesthesiologists will closely observe the respiration in the first few minutes after induction. Besides the first 3 minutes after induction, there were not any benefits for adding doxapram with induction agents by propofol and fentanyl. Therefore, it is rational to change the conclusion into "Adding doxapram on propofol and fentanyl combination presented less desaturation on the first 3 minutes after induction during painless gastrointestinal endoscopy".

Response:

Thanks for this valuable suggestion. All the anesthesiologists will closely observe the respiration in the procedure of painless gastrointestinal endoscopy. The clinical impact for injection doxapram with induction agents increased the SpO2 in the first 3 minutes and decreased the incidence of respiratory depression as well as respiratory treatment in our study. Decreasing the incidence of respiratory depression may bring safety to the patients and it’s meaningful
clinically. Decreasing the incidence of respiratory treatment may decrease the work of anesthesiologist.

Minor concerns

1. Page 4, line 65, please state your hypothesis.

Response:

Thanks for this valuable suggestion. We had stated the hypothesis in line 66-67.

2. Page 7, line 121, please define “respiratory depression” in a clear way. Is there tongue drop? Or hypoventilation? By their methods, airway obstruction seems to be the major reason for desaturation.

Response:

Thanks for this valuable suggestion. We defined “respiratory depression” in line 126 with reference. There may be both tongue drop and hypoventilation. Both will lead to respiratory depression. Airway obstruction which was caused by anesthetic is one of the reasons for desaturation.

3. Page 11, line 217, the depth of anesthesia?

Response:

Thanks for this valuable suggestion. Our mean is that doxapram doesn’t affect the quality of anesthesia although it works as an analeptic.

4. Figure 1, it is not necessary to use different symbols for statistical significance. P<0.05 is enough.

Response:

Thanks for this valuable suggestion. We have changed the same symbols for statistical significance according to the reviewer’s viewpoint. Please see the Figure 1.
5. Did your patients receive any anticholinergic such as hyoscinebutyl before gastroendoscopy? It will affect heart rate.

Response:

Thanks for this valuable suggestion. Patients in our study hadn’t received any anticholinergic such as hyoscinebutyl before gastroendoscopy aiming to eliminate its effect on heart rate.

RaikoBlondonnet (Reviewer 3): The submitted manuscript by Xin and colleagues shows that the use of Doxapram prevents respiratory depression induced by anesthesia in patients undergoing a gastrointestinal endoscopy.

Whereas the era of the topic seems interesting, I think the evidence to support this conclusion needs additional informations in order to improve the manuscript.

Major revisions

C1: I think the manuscript should be proofread very carefully by the authors in order to improve the readability. Thus, some sentences are in the wrong sections that its will be move.

Response:

Thanks for this valuable suggestion. We proofread the manuscript carefully and move some sentences in the wrong sections.

C2: Could the authors explain the specific inclusion criteria of age (i.e., between 26 and 68 years)? May be they would say "all patients > 18 years old"? If it is only the question of majority, the sentence "between 26 and 68 years" could be move in the section results.

Response:

Thanks for this valuable suggestion. We have changed the descriptions of inclusion criteria in accordance with the reviewer’s viewpoint in line 90. We moved the sentence “between 26 and 68 years” in the section results.

C3: Could the authors better explain the protocol? Indeed they write in the methods that oxygen was delivered at 3L/min. Was the flow rate of oxygen constant? Or before to use face mask/jaw lifting or ventilation, they increased the flow rate of oxygen. If the flow rate of oxygen was firstly increase, the authors should describe the SpO2 in function of the oxygen. The authors
should use the SpO2/FiO2 ratio. This important point should be clarified in the sections methods, results and discussion.

Response:

Thanks for this valuable suggestion. We have delivered oxygen at 3L/min in each patient to make the same oxygen concentration inhaled so that it will make the two groups to be compared under same trial condition. The flow rate of oxygen was constant in our study. We think that increasing the flow rate of oxygen before to use face mask/jaw lifting or ventilation is better and more reasonable according to the reviewer’s suggestion. SpO2/FiO2 ratio is more scientific and convicive. We will use the method suggested in the following works and studies. We added limitations in the paragraph before the section of conclusion.

C4: Did the authors have monitored postoperative pulmonary complications for the patients? If not, this point should be added as a limit.

Response:

Thanks for this valuable suggestion. We hasn’t monitored postoperative pulmonary complications for the patients and added as a limit in discussion before the section of conclusion.

C5: Did the authors have measured the time in PACU for each patient? Indeed this point could be interesting, especially if Doxapram could decrease the recovery time in PACU. This point should be add in the discussion.

Response:

Thanks for this valuable suggestion. We hasn’t measured the time in PACU for each patient and assessed with Aldrete–Kroulik modified index 30 minutes later. This point is interesting, especially if doxapram could decrease the recovery time in PACU. We added this point in the discussion.

C6: In order to improve the readability of the Figure 1, the author should be zoom the top of the 3 graphs. Thus the large ladder of the boxes hind the reader to see any difference between the
groups. Furthermore, the authors should explain if the boxes are with standard deviation, SEM, … and they should improve the legend of the figure.

Response:

Thanks for this valuable suggestion. I have changed the Figure 1, please see it.

C7: Did the authors assess the depth of anesthesia? The depth of anesthesia could partly explain the respiratory depression.

Response:

Thanks for this valuable suggestion. Unfortunately, we couldn’t describe the depth of anesthesia for the monitor lacking of this function. The depth of anesthesia such as bispectral index is important to guide the use of propofol. We added it in line 234-235.

C8: The statistics (i.e., first part of calculus of effective and second part of statistic test) in the section methods should be gathered.

Response:

Thanks for this valuable suggestion. We have gathered statistics in first part of calculus of effective and second part of statistic test in the section methods.

C9: In the section discussion, the paragraph of the effects of Doxapram on HR and MAP seems overinterpreted. The authors should nuance their meaning.

Response:

Thanks for this valuable suggestion. We have moved some sentences in the section of discussion to avoid overinterpreting the effects of doxapram on HR and MAP in line 223-224, 229-231.

C10: The authors need add a paragraph with limits in the discussion.

Response:

Thanks for this valuable suggestion. We have added a paragraph with limitations in the section of discussion in line 252-256.
The authors wrote "a third anesthesia nurse" but they did not explain where she was? And where were the one and second nurse? Could the authors clarify this point.

Response:

Thanks for this valuable suggestion. We have mistakenly described the anesthesia nurse as “a third anesthesia nurse“. Our primary meaning is to describe the anesthesia nurse as the third person except the patient and the anesthesiologist in charge of anesthesia. We had changed “a third anesthesia nurse“ into “an anesthesia nurse“ in line 108.

Minor technical comment

C11: Could the author clearly explain what is a "grade 3" hospital?

Response:

Thanks for this valuable suggestion. We have modified “grade 3” into “Grade III, Level A”. Our primary meaning is to describe the hospital as “Grade III, Level A” hospitals.

C12: Line 114 0.5mg/kg of what? We suppose that's propofol but the authors should clarify.

Response:

Thanks for this valuable suggestion. Line 114 0.05mg means fentanyl each patient. We have clarified in line 114 and 116 with “each patient” after “0.05mg”.

C13: Line 97 Miss space between about and sufentanil.

Response:

Thanks for this valuable suggestion. Line 97 we have modified space between about and sufentanil in line 103.

C14: Line 121 Miss space between oxygen and saturation.

Response:

Thanks for this valuable suggestion. Line 121 we have modified the sentence.
C15: Line 195 Miss space between doxapram and directly.

Response:

Thanks for this valuable suggestion. Line 195 we have modified space between doxapram and directly in line 203.

C16: Line 200 Miss space between we and speculate.

Response:

Thanks for this valuable suggestion. We have modified space between line 200 and speculate in line 213.

C17: Table 1 Miss space between BMI and (kg.m).

Response:

Thanks for this valuable suggestion. Table 1 has been modified space between BMI and (kg.m-2).