PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effect of propofol combined with opioids on cough reflex suppression in gastroscopy: study protocol for a double-blind randomized controlled trial
AUTHORS	Yin, Ning; Xia, Jiangyan; Cao, Yi-Zhi; Lu, Xinjian; Yuan, Jing; Xie, Jue

VERSION 1 - REVIEW

REVIEWER	Koo, Bon-Nyeo Department of Anesthesiology and Pain Medicine, Yonsei University College of Medicine, Seoul, South Korea
REVIEW RETURNED	27-Dec-2016

GENERAL COMMENTS	Recently, sedation anesthesia has been more important in modern medical practice. In the case of FOB (fibroptic bronchoscopy), cough is the main problem during the FOB procedure. However, cough is not considered as the major problem during gastroendoscopy. How much percentages of patients experience the cough during gastroendoscpy? What are the chief complaints after gastroendoscopy in your institution? Please, explain the primary endpoint in detail. How do you define the cough and the severity of cough? p. 3, 21 line, p. 7, 24 line: fentanil□ fentanyl p. 4, 21 line: key words: please include “cough” p. 4, 43 line: evaluate the antitussive effects of a wide range of opioids p. 7, 29: sedative performance, relieving stress and discomfort □ sedative performance p. 8 : could you include URI symptom, dry cough history, and drug allergy as the “Exclusion criteria” p. 9: we need more the evidence and reference about the dosage of sufentanil, dezocine, oxycodone. Why don’t your endoscipists in your institute use spay lidocaine? p. 10: Please, list up the expected adverse events. p. 10, 26-29: please, define the outcome related variables as well as variables that may influence the outcome until what time-point do you follow up your patient? (Such as until discharge of operating room, or discharge of PACU, or procedure after 1 day?.....) p. 11, 6 line: what is other discomfort? What is other side effect?

	When do you thrust jaw? and when do you assist ventilation ? What is the criteria about hypotension, bradycardia, hypopnea, apnea, desaturation? When dose your endoscopist insert the probe into your patients? How long after the administration of the study drug? Do you check the sedation level at the moment of insertion? I think that the same level of sedation is guaranteed at the moment of insertion. Don't your patients stay PACU?

REVIEWER	Rudy Noppens Western University, Canada
REVIEW RETURNED	06-Feb-2017

GENERAL COMMENTS	This is a clinically very relevant study examining the impact of several opioids on coughing and interventions needed to assure sufficient oxygenation during gastroscopy. Specific comments: 1) Please include a hypothesis to the abstract and the manuscript. I am sure the authors expect some superiority of one drug over the other. 2) Please address why the authors think that one drug is more superior to the other in this specific setting. 3) The authors decided on a high dose of Propofol for this study. This might have an impact on the research and might abolish the effects of the opioids examined in this study. The authors might consider using a lower dose of Propofol to have a clearer effect of opioids. 4) What is the actual incidence of coughing during gastroscopy? It is my impression that more patients present with gagging reflex. I suggest to include "gagging" to the study protocol. 5) The authors excluded patients with a BNMI > 30. Please address why they decided on this. This group of patients might profit from using smaller doses of Propofol in combination with an opioid. The authors already do a stratified randomization which also included BMI - which is great! Patients with a higher BMI could be quickly addressed. 6) The authors state that the anesthesiologist will be blinded to the study treatment. This raises the question who will inject the medication? Is there a way to identify the study group during the procedure in case of an adverse event? 7) I am not sure if sample seize calculation is correct. The expected effect must be huge if five different treatments are planned to compare with each other. What is the number of coughs which is expected for the control group? Please consider consulting a statistician in order to make sure that the calculation is correct. 8) Why is Propofol diluted with saline (page 8, line 52)?

	9) Please include who and how data is recorded for this trial. 10) Did the authors consider to include "patient satisfaction" as a secondary outcome? This is often the only parameter that is important for the patient undergoing gastroscopy. Because of the Propofol, I would think that many Patients can not recall coughing or gagging... Therefore it might not make a difference for the patient what approach has been used. Please address this in the manuscript. 11) There are some issues with punctuation and language in the manuscript. This can be easily solved.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. In the case of FOB (fibroptic bronchoscopy), cough is the main problem during the FOB procedure. However, cough is not considered as the major problem during gastroendoscopy.
Answer: We agree that cough is not a major problem. But it is one that can affect the procedure. We have found mechanical simulation may cause cough with inadequate sedation, leading to a difficulty of or even failure of endoscope insertion. The incidence of cough related to the drugs and the doses. We have used propofol alone in our hospital and the incidence of cough was about 30%. So we would like to perform such a study to find a way to solve this problem.

2. How much percentages of patients experience the cough during gastroendoscpy? What are the chief complaints after gastroendoscopy in your institution?
Answer: When propofol is used alone, about 30% patients experience cough and about 18% patient need to receive a second attempt of endoscope insertion after increasing the drug dose. Cough is indeed one of the chief complaints that are mainly from the endoscopists rather than the patients. Most patient can not recall coughing.

3. Please, explain the primary endpoint in detail. How do you define the cough and the severity of cough?
Answer: We have modified the endpoint as cough and gigging based on the suggestion of another reviewer. Cough usually occurs with inadequate sedation. The severity of cough is defined by cough intensity and whether leading to failure of endoscope insertion.

4. p. 3, 21 line, p. 7, 24 line: fentanil → fentanyl.
Answer: Done.

5. p. 4, 21 line: key words: please include “cough”.
Answer: Done.

6. p. 4, 43 line: evaluate the antitussive effects of a wide range of opioids.
Answer: Done.

7. p. 7, 29: sedative performance, relieving stress and discomfort → sedative performance
Answer: Done.

8. p. 8: could you include URI symptom, dry cough history, and drug allergy as the “Exclusion criteria”.
Answer: Done.

9. p. 9: we need more the evidence and reference about the dosage of sufentanil, dezocine, and oxycodone.
Answer: We had provide references for sufentanil and dezocine. But for oxycodone, we could not find more reference. The dose was decided based on our preliminary observation. There was only one references in Chinese for oxycodone:
X Liu, Z Quan, P Chi, et al. Comparison between oxycodone and sufentanil analgesia in anesthesia for gastroscopy, Beijing Medical Journal, 2016

10. Why don’t your endoscipists in your institute use spay lidocaine?
Answer: We use dyclonine, not spay lidocaine in our hospital. We have a large amount of patients in our hospital and doing so is to increase efficiency and reduce patients’ waiting time.

11. p. 10: Please, list up the expected adverse events.
Answer: Done.

12. p. 10, 26-29: please, define the outcome related variables as well as variables that may influence the outcome
Answer: Done. See the ‘Data collection and management’ section.

13. Until what time-point do you follow up your patient? (Such as until discharge of operating room, or discharge of PACU, or procedure after 1 day?.....)
Answer: Until discharge of PACU.

14. p. 11, 6 line: what is other discomfort? What is other side effect? When do you thrust jaw? And when do you assist ventilation? What is the criteria about hypotension, bradycardia, hypopnea, apnea, and desaturation?
Answer: We have explained these in the manuscript (see the ‘Sedation’ section).

15. When dose your endoscopist insert the probe into your patients? How long after the administration of the study drug? Do you check the sedation level at the moment of insertion? I think that the same level of sedation is guaranteed at the moment of insertion.
Answer: Indeed! We will insert the probe when BIS is 40-60.

16. Don’t your patients stay PACU?
Answer: ALL the patients stay PACU.

Reviewer: 2
1. Please include a hypothesis to the abstract and the manuscript. I am sure the authors expect some superiority of one drug over the other.

Answer: Done. Our hypothesis is that the combination of propofol and oxycodone may have a better performance than others.

2. Please address why the authors think that one drug is more superior to the other in this specific setting.
Answer: Oxycodone is an opioid analgesic acting on μ- and κ-opioid receptors, showing a good performance on relieving visceral pain with small respiratory depression effect as well as known to depress cough reflex.

3. The authors decided on a high dose of Propofol for this study. This might have an impact on the research and might abolish the effects of the opioids examined in this study. The authors might consider using a lower dose of Propofol to have a clearer effect of opioids.
Answer: Thanks! This is a very good point and indeed helpful! We have thought about that. However, the dose was decided based on our preliminary observation. We had chosen a lower dose in the combination groups. (Note that the dose for propofol alone in the figure 1 was wrong.) But to secure the success of endoscope insertion, we could not make the dose too low.

4. What is the actual incidence of coughing during gastroscopy? It is my impression that more patients present with gagging reflex. I suggest to include "gagging" to the study protocol.
Answer: When propofol is used alone, about 30% patients experience cough and about 18% patient need to receive a second attempt of endoscope insertion after increasing the drug dose. In our experience, gagging usually occurs with cough. But yes it is better to include gigging. We have modified the manuscript accordingly. Thanks!

5. The authors excluded patients with a BMI > 30. Please address why they decided on this. This group of patients might profit from using smaller doses of Propofol in combination with an opioid. The authors already do a stratified randomization which also included BMI - which is great! Patients with a higher BMI could be quickly addressed.
Answer: We totally agree the patients with a BMI > 30 might profit and we have thought about this point before setting up this protocol. However, our first concern is about recruitment. The BMIs of most patents we have are under 30. We also are not sure whether the pharmacodynamics is different in patients with higher BMI. So we determined to exclude the patients with a BMI > 30. However, we would like to conduct a study specifically in patient with higher BMI after this study.

6. The authors state that the anesthesiologist will be blinded to the study treatment. This raises the question who will inject the medication? Is there a way to identify the study group during the procedure in case of an adverse event?
Answer: The drugs will be prepared by nurse anesthetists and labeled with numbers. Then the anesthesiologist inject the medication. So the anesthesiologist will be blinded to the study treatment. The nurse anesthetists who prepare the drugs will not participate the operation but will be responsible for recoding. The anesthesiologist will be notified the study group by the nurse anesthetists in case of an adverse event.

7. I am not sure if sample seize calculation is correct. The expected effect must be huge if five different treatments are planned to compare with each other. What is the number of coughs which is expected for the control group? Please consider consulting a statistician in order to make sure that the calculation is correct.
Answer: This is a critical question! The sample size is estimated with our preliminary clinical experiences and we limited the sample size as possible due to the requirements of ethics. After consulting with a biostatistician, the sample sizes in the control and treatment groups should be around 100 based on cough incidence rate as 30% in the control group and effective size as 20%. So we have increase the sample size to 100.

8. Why is Propofol diluted with saline (page 8, line 52)?
Answer: We are sorry that this is incorrect. It should be drugs except Propofol.

9. Please include who and how data is recorded for this trial.
Answer: Done. Data are recorded automatically by the vital signs monitor and anesthesia information system, and manually by a nurse anesthetist.

10. Did the authors consider to include "patient satisfaction" as a secondary outcome? This is often the only parameter that is important for the patient undergoing gastroscopy. Because of the Propofol, I would think that many Patients can not recall coughing or gagging... Therefore it might not make a difference for the patient what approach has been used. Please address this in the manuscript.
Answer: We did not consider to include "patient satisfaction" as a secondary outcome. The reason is indeed as you said. We do not think the approach will make a difference since patient can not recall coughing or gagging. We have modify the manuscript accordingly.

11. There are some issues with punctuation and language in the manuscript. This can be easily solved.
Answer: Thanks! We have improved the language.

VERSION 2 – REVIEW

REVIEWER	Ruediger Noppens Department of Anesthesia and Perioperative Medicine, Western University, Canada
REVIEW RETURNED	18-May-2017

GENERAL COMMENTS	I think a limitation of this study is the Propofol dose used. Please include this in the "Strengths and Limitations" section of the manuscript. Measuring BIS is an excellent tool to show that all groups examined have a comparable depth of sedation. A BIS of 40-60 is usually considered as sufficient depth of "general anesthesia." I think this should be pointed out in the manuscript. I do not expect that this will be a significant problem since the authors plan to measure the incidence assisted ventilation. Please make sure that all abbreviations (e.g "PACU", page 34, line 42) are fully explained.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
1. I think a limitation of this study is the Propofol dose used. Please include this in the "Strengths and Limitations" section of the manuscript.
Answer: Done. We agree this is indeed a limitation.

2. Measuring BIS is an excellent tool to show that all groups examined have a comparable depth of sedation. A BIS of 40-60 is usually considered as sufficient depth of "general anesthesia." I think this should be pointed out in the manuscript. I do not expect that this will be a significant problem since the authors plan to measure the incidence assisted ventilation.
Answer: Done. Thanks for pointing out!

3. Please make sure that all abbreviations (e.g "PACU", page 34, line 42) are fully explained.