Author’s response to reviews

Title: Optimal dose of pretreated-dexmedetomidine in fentanyl-induced cough suppression: a prospective randomized controlled trial

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Author’s response to reviews:

First of all, we would like to express our sincere gratitude to the reviewers for their constructive and positive comments and suggestions.

Replies to Reviewer 1

1. In the study the authors used very high doses of fentanyl (4 mcg / kg). You affirm that this is the dose that you normally use in your daily clinical practice. Don't you think it's too high? In a time when all efforts are aimed at reducing the amount of opioids used during anesthesia, this dose is, in my opinion, excessively high. In daily clinical practice in our center, we use much lower doses (0.8-1 mcg / kg) and fentanyl-induced cough is an extremely rare event. In addition, all studies performed on the subject have shown that an independent risk factor for fentanyl-induced cough is the administered dose.
Response: Thank you for your insightful comments. In fact, the dose of fentanyl 4 mcg/kg is used conventionally for general anesthesia (GA) induction in our clinical practice, which is also consistent with its recommended dose (2-6 mcg/kg) for GA induction in Miller’s Anesthesia (7th edition). We do agree with you that we should pay more attention to the side effects of excessive use of opioids. We also tried lower doses (1 or 2 mcg/kg) for anesthesia induction, but sometimes the hemodynamic fluctuations during intubating or at the beginning of surgery due to stress have bothered us. So, we selected the dose of fentanyl 4 mcg/kg for GA induction except patients of ASA classified higher than II, who were already excluded from the current study.

2. The authors state that this is a double-blind study. They should better describe how this study was conducted. A double-blind study predicts that those involved in the study are completely unaware of the group to which the patients belong. Please clarify better how this condition has been achieved.

Response: Thank you for your thoughtful comments. The study was double-blind. Actually, the patients were assigned to four groups using computer-generated random numbers, which was already highlighted in green in line 16 on page 4. Also, all the pretreatments were prepared and implemented by an experienced anesthesiologist who was not involved in data collection, which was highlighted in green in lines 2-4 on page 5. All the priming drugs and the infusion pumps were covered with a piece of sheet, also highlighted in green in lines 4-5 on page 5, so the anesthesiologist who recorded the data could not get any indication of the pretreatments. The recording of fentanyl-induced cough was done by an anesthesiologist who was unaware of the grouping criteria, which was highlighted in green in lines 17-18 on page 5. Also, we added the information that the recording of side effects after pretreatments in each group were done by another anesthesiologist who was unaware of the grouping criteria, which was added and highlighted in yellow in lines 1-2 on page 6.

3. How were the different doses of dexmedetomidine decided? Do you have a previous clinical experience? Do you have any literature data? Please clarify.

Response: The different doses of dexmedetomidine were decided on the basis of our previous clinical experience and recent literatures. The recommended dose of dexmedetomidine to achieve its steady state plasma concentration is 0.5-1 mcg/kg over 10 mins in its Drug Instruction. In our previous clinical experience, we used the dose of 0.05 mcg•kg-1•min-1 for 10 mins’ infusion and found that the fentanyl-induced cough was alleviated to a certain extent. In Yu J et al.’s study [Ir J Med Sci 2012, 181(4):517-520], the authors found that dexmedetomidine 0.6 mcg/kg combined with midazolam 0.06 mg/kg could suppress FIC more effectively than dexmedetomidine 0.6 mcg/kg alone with the infusion time of 10 min. In their study, they injected fentanyl in 2 s, which might be too fast injected and not suitable in clinical practice. We
speculated that dexmedetomidine 0.6 mcg/kg with the infusion time of 10 min would be effective in suppression of fentanyl-induced cough when fentanyl was injected with a slower speed, and wondered that whether smaller or bigger dose of dexmedetomidine could effectively alleviate fentanyl-induced cough without side effects. So, we selected the multiple doses of 0.3, 0.6 and 0.9 mcg/kg over 10 mins in our study.

5. The whole discussion seems confusing, it would probably be more effective if it were shorter.

Response: Thank you for your insightful comments. We have shortened the discussion part according to your suggestion and the relevant changes we have made are wrote in red in lines 27-28 on pages 7.

Replies to Reviewer 2

1. Methods: Overall methods are good; however, please define hypotension and impairment of liver and kidney function parameters/criteria.

Response: Thank you for your thoughtful suggestion. “Hypotension” here in our study was defined as blood pressure < 90/60 mmHg, which was added and highlighted in yellow in line 10 on page 5. To speak of the determination of liver and kidney function impairment, we mainly rely on the patients' past or current disease history (such as chronic hepatitis or chronic nephritis) and relevant biochemical indicators (such as ALT, AST, DBIL, ALB, creatinine and urea nitrogen, etc.).

2. Are the conclusions drawn adequately supported by the data shown: Yes; however, the paper needs better organization regarding MAP and HR (safety) in the results section. MAP and HR significance is stated for group 4 at various time points. It would be worth additional clarification in the Results section to state nonsignificance in the groups 1, 2, and 3 regarding HR at all time points compared to T0. You did make that point in the discussion "There were no significant changes of MAP, HR, or SpO2 occurred in the other three groups" but clarification is needed in the Results section.

Response: Thank you for your insightful suggestion. The changes of MAP and HR in groups 1, 2, and 3 were supplemented in the safety part in lines 13-17 on page 7, which is highlighted in yellow.
3. Extensive Language editing will be required to make the paper flow smoothly and unambiguously

Response: Extensive language editing has been done according to your good suggestion.

Other Comments:

1. The word "pumped" is used often and should be changed to intravenous, bolus, etc depending on the context.

Response: Good suggestion! Changes have been made in lines 6 and 26 on page 2, line 27 on page 4, line 23 on page 7, and line 1 on page 10, which were highlighted in yellow.

2. Background:

line 33- need to change phrase "to hinder or relieve this side effect" as it doesn't flow well

Response: "to hinder or relieve this side effect" was replaced by “to decrease or eliminate this adverse effect”, which were highlighted in yellow.

line 37- the phrase adrenoceptor "excitatory effect" is used often throughout the paper. I would consider changing to "agonist effect"

Response: "agonist effect" is really more appropriate according to the meaning of the sentence, and changes have been made in line 18 on page 3.

line 47- states that another study does not exist regarding optimal dose of dexmedetomidine (Dex), this is not entirely correct- please cite and review: Liang He, Jun-Mei Xu, Ru-Ping Dai. Dexmedetomidine reduces the incidence of fentanyl-induced cough: A double-blind, randomized, and placebo-controlled study. Ups J Med Sci. 2012 Mar; 117(1):18-21. Better cough suppression was found at 1 mcg/kg bolus vs. 0.5 mcg/kg Dex bolus without an increase in side effects.

Response: Thank you for your insightful suggestion. The literature was cited and reviewed according to your suggestion. In the above literature, patients were given different doses of dexmedetomidine diluted with isotonic saline to 10 mL intravenously infused over 10 mins, and better cough suppression was found at 1 mcg/kg vs. 0.5 mcg/kg dexmedetomidine bolus without an increase in side effects. It is a meaningful clinical trial. While we are wondering that how to control the time of 10 min for a 10 mL fluid intravenous injection without an infusion pump? In
our study, we applied infusion pumps to control the dose of pretreated dexmedetomidine. We found in our preliminary study that dexmedetomidine 1 mcg/kg over 10 mins sometimes caused decreased HR or respiratory depression, which might be dangerous to patients. The doses of 0.3 mcg/kg, 0.6 mcg/kg and 0.9 mcg/kg over 10 mins were selected in our study based on our preliminary study and recent study [Ir J Med Sci 2012, 181(4):517-520].

3. Study protocol: I would consider changing dex dosing information to "mcg/kg bolus given over 10 minutes" as this is how it is typically written in similar studies. The current description: mcg/kg/min for 10 minutes is technically accurate but not the typical manner that dex bolus dosing is usually described.

Response: Thank you for your thoughtful suggestion. We have changed dex dosing information to “dexmedetomidine mcg/kg bolus given over 10 mins”.

4. Sample size determination: line 3- why did you hypothesize that incidence of FIC would be reduced to 15% ?

Response: In our preliminary study, the incidence of FIC was 48% in the control group. It means that nearly one-half patients had FIC. In previous studies, the incidences of FIC were reduced to lower than 15% with significant difference. We think that it would be of great significance if the FIC incidence reduced to 15% in our study. So, we hypothesized that incidence of FIC would be reduced to 15% after certain dose of 10 mins’ dexmedetomidine priming infusion.

5. Effects of pretreatments on the onset time of cough: line 13- need to add information to table 2 regarding onset time of cough

Response: Information regarding onset time of cough has been added to table 2.

6. Safety: this paragraph needs more HR information. Please separate HR information from MAP information from adverse event information- it is a little unclear as written. See comments above related to conclusion, need some more detail on comparisons in safety section pertaining to HR for groups 1, 2, and 3.

Response: Thank you for your insightful suggestion. The changes of MAP and HR in groups 1, 2, and 3 were supplemented in the safety part in lines 13-17 on page 7, which were highlighted in yellow.
7. Discussion:

line 15- "as compared to 'lower doses' in the previous studies" did you mean to state "slower injection"?

Response: No, “lower doses” means doses lower than the dose of 4 mcg/kg in our study. In both previous studies (Anaesthesia. 2007 Dec; 62(12):1230-2; Anesth Analg. 2004 Dec;99(6):1696-8), 3 mcg/kg of fentanyl was injected over 5 s. To avoid confusion, we have changed the sentence to “A higher incidence of cough occurred in our control group than in some previous reports [4, 17], which was probably due to the rapid injection of fentanyl bolus (5 s of 4 mcg/kg) in our study”.

line 21- mechanism of FIC- need citations for mechanism (3) and (4)

Response: Thank you for your thoughtful suggestion. Citations have been added for mechanisms (3) and (4).

line 9- need citation for suppression of FIC by penetration of blood brain barrier and inhibiting cough center directly

Response: The relevant citation has been added.

line 17- "Prolonging the injection time of fentanyl over the time to reach the threshold of its plasma concentration may reduce the incidence and severity of FIC further, which is our next work to be done"- it is already known that extending the time of administration of fentanyl will reduce incidence of cough

Response: Thank you for your insightful suggestion. The sentence has been changed to “Prolonging the injection time of fentanyl over the time to reach the threshold of its plasma concentration could reduce the incidence and severity of FIC further”, which was highlighted in yellow.

line 23- please rewrite the following sentence to make it flow better: "First, judging measures. . . and no more accurate indicators have been found till now".
Response: Thank you for your good suggestion. The sentence has been changed to “the judgment index of FIC incidence and degree is subjective, for no objective indicators have been found till now”, which is highlighted in yellow.

8. Table 1: the Numbers row is not essential. That info is already in the table. Also the term "Figure Legends" above Table 1 needs to be deleted.

Response: We have deleted the Numbers row and “Figure Legends” according to your suggestion.

9. Table 2: please add cough onset time data as a new row, this is important data.

Response: Cough onset time data has been added as a new row in Table 2.

10. Figure 1: add "refused to participate" after "5 did not meet the inclusion criteria and 7".

Response: Thank you for your careful review. It was our carelessness that the text box was not adjusted to the appropriate size, causing “refused to participate” after “7” not to be shown. "refused to participate" was added after “7”.

11. Figure 2 and 3: T3 needs to be defined below both figures. Please clarify precisely that p-values (a,b) pertain to group 4 (this seems to be the intent).

Response: The definition of T3 has been added below Figures 2 and 3. It seems that the previous Figures 2 and 3 were too messy, so we recreated new Figures for better demonstration of the data.

Reviewer 3

The main criticism of this study in my opinion is the missing scientific approach. It is more scientific to elucidate why an increase in synthetic opioid blood concentration induces a cough, instead of conducting studies about reducing its clinical frequency. The frequently associated induction of cough is usually neither harmful for the patient nor bothersome. Promising strategies in order to achieve the aim of cough suppression consist for instance of decreasing the injection speed in conjunction with pre-administration of lidocaine. In a recent meta-analysis Wu et al. (Int J Clin Exp Med 2016;9(5):7655-7667) published that the lowest effect dose of
Response: Thank you for your comments. Synthetic opioid is essential for general anesthesia induction, although cough may be induced. The causes have been elucidated in our manuscript in the discussion part. Conducting studies to decrease fentanyl-induced cough (FIC) is also important because the cough can be explosive and detrimental especially in patients with increased intracranial, intraocular, intrathoracic, or intra-abdominal pressure. FIC could even cause severe upper airway obstruction and aspiration pneumonia that require immediate intervention. A report that explosive FIC produced multiple conjunctival and periorbital petechiae has been published. FIC needs immediate and effective intervention especially in patients with cerebral aneurysm, brain trauma, hernia, open eye injury, dissecting aortic aneurysm, pneumothorax or hypersensitive airway disease. Precaution of FIC in these situations is of great importance. Various strategies have been investigated to decrease FIC, among which lidocaine might be an option. But it is not suitable for patients with high local anesthetic sensitivity. Dexmedetomidine may be a good choice to decrease FIC.

In the meta-analysis, Wu et al. (Int J Clin Exp Med 2016;9(5):7655-7667) published that the lowest effect dose of dexmedetomidine for preventing the prevalence of OIC was 0.1 μg/kg. We have reviewed the studies using dexmedetomine 0.1 mcg/kg in this meta-analysis. In one of the studies (J Anesth. 2013 Feb;27(1):25-8), dexmedetomidine was added to 10 mL normal saline and at a steady rate of 2 ml/min. According to the instructions and clinical experiences of dexmedetomidine before anesthesia, it is often used at doses of 0.5-1 mcg/kg over 10-15 mins. We doubt whether pretreatment of dexmedetomidine 0.1 mcg/kg intravenous infusion within 5 mins could achieve a steady plasma concentration. So, we investigated the optimal dose of dexmedetomidine to decrease FIC effectively without side effects in the current study.