Author’s response to reviews

Title: Efficacy of premedication with intranasal dexmedetomidine for removal of inhaled foreign bodies in children by flexible fiberoptic bronchoscopy: a randomized, double-blind, placebo-controlled clinical trial

Authors:

Yanmei Bi (1164197332@qq.com)
Yushan Ma (mayushan_123@163.com)
Juan Ni (nijuanwiki@163.com)
Lan Wu (Lwu2019@163.com)

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Dear Editors and Reviewers:

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “Efficacy of intranasal dexmedetomidine for removal of inhaled foreign bodies in children by flexible fiberoptic bronchoscopy: a randomized, double-blind, placebo-controlled clinical trial” (ID: BANE-D-19-00086). Those comments are all valuable and very helpful for revising and improving our paper. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. The main corrections in the paper and the responds to the reviewer’s comments are as flowing:

Responds to the reviewer’s comments:

1. Response to comment:(Data are analysed with parametric statistics. Are authors sure of the normal distribution? This should be verified otherwise median (IQR) and non-parametric stat should be used)
Response: We are very sorry for our errors in statistical methods. We have carefully checked the data, except for duration of foreign body aspiration, time-lag between diagnosis and removal of foreign body, oxygen saturation, duration of anesthesia induction, duration of procedure, extubation time, and recovery time, all of them conform to normal distribution. median (IQR) and Wilcoxon’s rank-sum test were used for analyze duration of foreign body aspiration, time-lag between diagnosis and removal of foreign body, oxygen saturation, duration of anesthetic induction, duration of procedure, and extubation time, and recovery time.

2. Response to comment: (Groups should be directly identified rather than using letters (this may be confusing for the reader))

Response: We are very sorry for the confusing caused by using letters to identified groups. We have identified the groups directly. DEX group: patients who was given dexmedetomidine pre-anesthesia, and control group: patients who was given saline pre-anesthesia.

3. Response to comment: (Some main data may be better presented in graphs rather than in tables.)

Response: We are very grateful to the reviewer for his/her suggestion. The adverse events and BIS values previously presented in Table 2 and Table 4, are now show in Figure 4 and Figure 6.

4. Response to comment: (Undoubtedly, the interest of DEX is especially high for infants and small children: this should be commented in discussion and identified as future research steps.)

Response: This new anesthetic agent, used alone at clinical doses, has not induced neurotoxicity in juvenile animal models. It exhibits neuroprotective effects in vitro and attenuates neuro-apoptosis caused by other anesthetic agents. It is thus considered one of the rare “neuro-safe” anesthetic agents used in infants.

5. Response to comment: (TITLE—It could be misleading as it is; at least "premedication" should be added, otherwise it might seem that dexmedetomidine is the only agent used.)
Response: We are very sorry for the misleading in Title. We have added “premedication” in title, and noted that dexmedetomidine used as premedication in title and the main text.

6. Response to comment: (The paper premises are someway misleading: there is no debate weather flexible or rigid bronchoscopy is better for inhaled foreign body removal, especially in pediatric patient. Flexible bronchoscopy is a precious tool for diagnosis, especially of radio-transparent foreign bodies, and it might allow also their removal, providing an adequate ventilation is maintained (i.e. through a supraglottic device). Nevertheless, due to small fiberoptic caliber allowed in pediatric patients, sometimes the same aspiration is challenging, and size of operative tools (forceps, canister..) sometimes is too large to be used in (small diameter) scopes. Thus, rigid bronchoscopy Cannot be substituted for these procedures, particularly considering that it also allows oxygenation (Jet).

So, definitively, I would not consider as a comparison between two alternative techniques, but rather as two complementary tools for a really challenging procedure.)

Response: We are very sorry for the misleading caused by the content about the comparison about rigid bronchoscopy and flexible fiberoptic bronchoscopy. We also believe that rigid and flexible bronchoscopy are two complementary tools for foreign body removal. There is no otolaryngologist in our hospital, no rigid bronchoscopy for foreign body removal. Doctors of our hospital are more familiar with flexible fiberoptic bronchoscopy, more skilled fiberoptic bronchoscopic airway foreign body removal.

7. Response to comment: (During the removal procedure, it is also extremely important to induce adequate reflexes blunting, due to high risk of airway lesions (especially if a rigid scope is used) and my personal experience is that dexmedetomidine alone might not be enough to allow the procedure safely. Foreign body removal is a totally different practice if compared with diagnostic flexible endoscopy (time, duration, respiratory status, possible complications.). If, as in the research from Yanmei, it is combined with sevoflurane, probably small (reduced) doses of opioid analgesic could be considered; Line 83: completely true, but this also depends on anesthetic depth and on use of opioids as reflex-blunting medications; I can't see the benefit of dexmedetomidine not inducing respiratory depression, ventilation granted by LMA. Different centers do use neuromuscular blocking agents for this procedure.)
Response: Fiberptic bronchoscope has less airway irritation, the use of foreign body basket significantly shortens the time required for foreign body removal. So it is possible that sevoflurane VIMA for fiberoptic bronchoscopy foreign body removal under spontaneous breathing, without opioids and muscle relaxant. In addition, Ren L, et al reported that sevoflurane VIMA anesthesia for rigid bronchoscopy under spontaneous breathing provides more stable hemodynamic and respiration, faster recovery. Remifentanil may inhibit respiratory rate. Mechanical ventilation required in patient who was given remifentanil and muscle relaxants. Spontaneous ventilation provides better ventilation/perfusion ratio, more effective alveolar ventilation and lack of ventilation associated lung injury. Maintains spontaneous ventilation is commonly practice to minimize the risk of converting a partial proximal obstruction to a complete obstruction.

8. Response to comment:( How was the 1 mcg/kg dose defined? Line 271 does not seem to report adequate explanation. Other papers report higher doses ranging (2 to 3 mcg/kg))

Response: It is reported that plasma concentrations of dexmedetomidine approached 100pg·ml-1 (the low end reported for sedative efficacy) within 20 mins of an atomized intranasal administration of 1 mcg·kg⁻¹ dexmedetomidine in children, thereby producing satisfactory sedation before anesthesia induction. Indeed, our preliminary results showed that dexmedetomidine 1 mcg·kg⁻¹ produces a satisfactory sedative effects without prolonged recovery time, whereas a 2 mcg·kg⁻¹ or higher dose of dexmedetomidine significantly prolong the recovery time.

9. Response to comment:( Line 132: CO₂ is measured by capnography, not EtSevo. Authors are probably referring to sidestream sampling, probably infrared absorption technology.)

Response: We are very sorry for the mistake. The EtCO₂ was measured by a capnography sensor placed between the L-piece and Bain circuit. The Etsevo was measured by side-stream sensor placed at the breathing circuit filter.

10. Response to comment:( Size of used fiberoptic scope and LMAs should be reported.)
Response: We are very sorry for not reporting the size of fiberoptic and LMAs at manuscript. We have reported the size of fiberoptic and LMAs at Table 5.

11. Response to comment: (Removal means of foreign body should also be noticed, and similarly time-lag between diagnosis and retrieval of foreign body, as time lag might severely influence complications and outcome due to different airway reactivity and inflammation)

Response: We are very sorry for not reporting the removal means of foreign body and time-lag between diagnosis and retrieval of foreign body. We have described the means of foreign body removal in method section, and Figure 2. Time-lag between diagnosis and retrieval of foreign body was reported in table 3.

12. Response to comment: (How many patients received extra medication? i.e. remifentanil or propofol? Was also cortisone or other medication administered? Authors mention acetylcysteine line 245.)

Response: We are very sorry for not reporting the use of extra medication. We have reported the number of patients received extra medication and the dosage in Table 5.

13. Response to comment: (Also the choice for anesthetic gas vs intravenous propofol as anesthesia maintenance technique for inhaled foreign body removal should be discussed, due to literature controversial and evidence.)

Response: Some previous reports showed that propofol as anesthesia maintenance for inhaled foreign body removal had a higher incidence of breath holding, cough, and desaturation, and a delayed recovery. Compared with TIVA, sevoflurane VIMA provides better hemodynamic characteristics and more stable respiratory for FB removal in children.

14. Response to comment: (On which endpoints or difference was power analysis calculated? 20 patients per study arm are a limited number of cases.)
Response: The endpoints for power analysis calculation was laryngospasm. The sample size was calculated based on the ability to detect a 44.4% reduction in the incidence of laryngospasm with dexmedetomidine premedication (55.6% vs 11.1%, according to our preliminary study) with 80% power. The level of significance was set at two-sided $\alpha = 0.05$. It was then concluded that the sample size required to achieve a statistically significance was 20 for each group.

15. **Response to comment:** (How do you explain differences in reactions, movements, hemodynamic parameters, spontaneous breath between two groups given a non-significant BIS value difference?)

Response: Dexmedetomidine is useful in reducing the airway irritation during fiberoptic bronchoscopy via its unique analgesic effect. Although, there was a non-significant difference in BIS value between the two group, the incidences of body movement, coughing and laryngospasm were lower in patient receiving dexmedetomidine. The lower HR during the study period in DEX group might be explained by the decreased sympathetic outflow and circulating levels of catecholamines caused by dexmedetomidine. In our study, premedication with dexmedetomidine reduced the consumption of sevoflurane, propofol and remifentanil. So the respiratory rate more stable in patient received dexmedetomidine.

16. **Response to comment:** (Line 255: unclear. Difference in RR was then due to (relatively) higher Sevoflurane concentration in group C or because of dexmedetomidine apnea-sparing effect in group D?)

Response: The difference in RR between the two group might associated with the higher concentration of sevoflurane and more consumption of propofol and remifentanil in control group. Moreover, respiratory rate, CO2 retention, and oxygen saturation are generally maintained during dexmedetomidine sedation in children.

17. **Response to comment:** (Line 283: what is meaning for bilateral bronchus?)

Response: bilateral bronchus is both right and left bronchus.
18. **Response to comment:** (Table 5, unclear: what is "extubation time"?)

Response: Extubation time was defined as the time from discontinued sevoflurane to LMA removal.

19. **Response to comment:** (references need to be updated.)

Response: We are very sorry for not updating the references. We have carefully checked and updated the reference.

20. **Response to comment:** (English shall be revised by a native English speaking colleague or a professional service; Line 71: fetal (?) fatal Line 219 principle -&gt; principal Line 242 precious previous )

Response: We are very sorry for our language mistakes. We have carefully reviewed the language and grammatical issues and corrected by an English-language expert.

We appreciate for Editors/Reviewers’ warm work earnestly, and hope that the correction will meet with approval.

Yours sincerely,

Lan Wu