Author’s response to reviews

Title: A randomized trial to evaluate a modified tracheal catheter with upper and lower balloons for anesthetic administration: effect on the cardiovascular, stress response, and comfort in patients undergoing laparoscopic cholecystectomy

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Author’s response to reviews:

Dear Dr. Alessandro Belletti and editorial board,

Thank you very much for your decision letter and constructive advice pertaining to our manuscript (Manuscript BANE-D-19-00173R3) entitled “Randomized trial to evaluate a new tracheal catheter with upper and lower balloons for anesthetic administration: effect on cardiovascular, stress response, and comfort in patients undergoing laparoscopic cholecystectomy”. We have revised our manuscript according to your suggestions (as highlighted in the revised manuscript). In addition, point-by-point responses to the comments are listed below this letter.

We hope that the revised manuscript is acceptable for publication in your journal.

Look forward to hearing from you soon.

With best wishes,

Yours sincerely,

Zhiwen Zeng
Reviewer reports:

Praveen Chahar (Reviewer 1): Thanks for making the changes in manuscript

Hossam El-Beheiry (Reviewer 2):

This is the third revision of the manuscript entitled 'A randomized trial to evaluate a new tracheal catheter with upper and lower balloons for anesthetic administration: effect on the cardiovascular, stress response, and comfort in patients undergoing laparoscopic cholecystectomy.' Unfortunately, there are still few outstanding issues with the manuscript:

1. The rational for the small sample size is not convincing.

Reply: Thanks for the comment. We agree that 90 is not a large sample size. The sample size was decided based on the following two considerations: (1) We tested a modified endotracheal tube with no previous clinical experience to be referred to. Therefore, an experiment even with a limited sample serves as a valuable pilot trial. (2) Relevant studies (including the two studies cited below) were referred to before designing this study; these had sample sizes of 60 and 62, respectively.

In this context, we believe that it is reasonable to start with a small sample size.

Also, the study is registered in the Chinese Clinical Trial Registry in January 2019 (http://www.chictr.org.cn/index.aspx) (Registration Number: ChiCTR1900020832). Currently, the study has been completed and closed. Therefore, it can be difficult to add further cases into the existing database.

Associate Editor: please add the small sample size to study limitations

Reply: Thanks for the comment. The small sample size has been acknowledged as a study limitation in the discussion section as highlighted in the revised manuscript.

2. Post-operative hemodynamic data cannot be taken into consideration because of the administration of atropine and neostigmine at the end of surgery to reverse the muscle relaxation.

Reply: Thanks for the comment. According to the study design, atropine and neostigmine were provided at the end of surgery at the same dosage and the same time-point to all the included patients. This procedure is also part of the routine operative protocol at our hospital. Therefore, parallel comparison among the three groups of patients was feasible since the effects of the same post-operative medical treatment were experienced identically in all patients.

Associate Editor: please discuss this issue – as in the reply to Reviewer – in the discussion
Reply: Thanks for the comment. The response has been added in the discussion section as highlighted in the revised manuscript.

3. The first paragraph of the introduction is irrelevant to the rational of the study. Measuring the stress response of a newly designed endotracheal tube during induction is irrelevant to the surgical procedures.

Reply: Thanks for the comment. The first paragraph of the introduction section has been revised (as highlighted in revised manuscript). We briefly mention the wide use of laparoscopy in clinical practice and the associated cardiovascular complications, just to highlight the importance of improving general anesthesia in order to minimize the circulatory side effects. According to the study design, blood parameters were used as an alternative to pressure to reflex cardiovascular response.

Associate Editor: the reply and manuscript editing are overall fine. However, the Authors actually measured blood pressure. This part is unclear to me

Reply: Thanks for the comment. Sorry for not clarifying this aspect. We did measure the blood pressure here as an indicator of hemodynamics during intubation. The lesser the laparoscopy-induced hemodynamic derangement, the lesser will be the risk of cardiovascular complications, which make it easier for the patients to tolerate the subsequent surgical procedure. That is why it is important to improve the laparoscopic technique to achieve better surgical outcomes; this in fact underlines the clinical relevance of our study.

4. Still, there is no clear hypothesis stated at the end of introduction section to clarify what issue has been tested and state the primary outcome of the study.

Reply: Thanks for the comment. L75-84 in the original manuscript has been moved to the first paragraph of the Discussion section. The hypothesis has been revised as shown in the last paragraph of the Introduction section (highlighted in the revised manuscript) to better clarify the primary goal and outcome of this study.

Associate Editor: the reply and manuscript editing are overall fine.

5. Measurement of Angiotensin II has not been shown previously to increase during laryngoscopy and intubation (EJA 22(10):780-785, 2005). The rational of measuring Angiotensin II and blood sugar as a measure of stress response is not substantiated. It was more appropriate to measure plasma catecholamines.

Reply: Thanks for the comment. Actually we have explained the rationale for the detection of angiotensin II as a biomarker in the original manuscript briefly: “Under general anesthesia, tracheal intubation excites the renin-angiotensin system and increases the level of angiotensin II.
Therefore, the concentration of angiotensin II can be used as a specific indicator of the intubation-induced stress response. Moreover, glycogenolysis and gluconeogenesis are upregulated under these conditions, causing an increase in blood glucose concentration. Therefore, the level of angiotensin II and blood glucose were measured as quantitative parameters of the degree of irritation caused by endotracheal intubation.”

During literature search, we also found studies that have used Ang II as a parameter reflecting hemodynamic variation during tracheal intubation. Some are listed below:


Coriat, P. "Interferences between angiotensin-converting enzyme inhibitors and spinal anesthesia." Cahiers d'anesthesiologie 42.6 (1994): 727-733.


Based on these, we believe there is adequate rationale to support the use of Ang II as a marker of stress response.

Associate Editor: the reply is fine. Please add this paragraph, as well as the cited references, to the Discussion

Reply: Thanks for the comment. Necessary changes had been made in the discussion section as highlighted in the manuscript.

6. The Murphy opening in any regular endotracheal tube provides an alternative port of ventilation if the tip of the tube is partially or completely obstructed. Any custom-made endotracheal tube which doesn't have a Murphy opening may lead to a situation of compromised safety pertaining to adequate ventilation. The tube studied in the manuscript has micro-openings instead of the Murphy opening. These micro-opening cannot be considered to be a safe alternate route for ventilating the trachea if the tip of the tube is occluded by secretion or by resting against the wall of the trachea. The manuscript doesn't comprehensively discuss this issue. Measuring of the airway resistance as done in this study is not a measure for the safety of a tube without a Murphy opening. The manuscript does not mention how much ventilation can be achieved through the micro-openings and whether the ventilation is efficient.

Reply: Thanks for the comment. When selecting patient for the study, patients with lung disease were excluded, considering that such patients may secrete more sputum, causing blockage of
micropores. This is also additionally described in the "General materials" subsection of the "Methods" section (L114-116).

In the conventional design, a drug delivery bag is located at the end of the cuff, the wall of which adheres to the endotracheal tube. The drug delivery bag, along with the single Murphy eye at the end, extends the length of the endotracheal tube, which increases the risk of displacement and may potentially adversely simulate the tracheal carina.

The main purpose of our design modification is to reduce the tube length by replacing the single Murphy eye with a group of minipoles. The total area of these holes is equivalent to the area of the original Murphy eye; therefore, ventilation can be ensured.

The modified design features with reduced tube length and easy manufacturing process.

In the present study, we evaluated the safety and efficacy of the new intratracheal catheter in patients undergoing laparoscopic cholecystectomy by monitoring the cardiovascular parameters including systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), angiotensin II, and blood glucose levels. The pain experience and adverse events were also monitored. Our data demonstrates the safety and performance of the modified design.

Associate Editor: I think the Authors’ reply in this case in not adequate. Please add a paragraph in the Discussion underlying this important potential limitation and risk of new endotracheal tube. I suggest to perform a bench/manikin study testing the capability of the new tube to ensure ventilation during artificial occlusion.

Reply: Thanks for the comment. The limitation of the new intratracheal catheter, especially the safety concerns, have been acknowledged in the discussion section as highlighted in the manuscript. Further study is required to assess its safety.

7. The manuscript has to clarify that the newly invented tube will not obtund the stress response to laryngoscopy, but such tube may depress the stress response to the introduction of the tube into the trachea and pre-extubation coughing and increases in BP and heart rate.

Reply: Thanks for the comment. As has been mentioned in the manuscript, the development of the two-channel multi-hole system differentiates the newly invented tube from the conventional tube; this helps achieve better intratracheal surface anesthesia during intubation and extubation. As intratracheal surface anesthesia was applied only during the introduction of the tube into the trachea and immediately prior to extubation, intubation or extubation related stress response can be better alleviated by our newly invented tube.

Associate Editor: Again, I am not satisfied with the reply. Please add in the limitation a section describing that the new tube will not blunt sympathetic response to direct laryngoscopy
Reply: Thanks for the comment. This issue has been addressed in the discussion section, as highlighted in the manuscript.

8. How the lidocaine 2% was sprayed in group B? What are the structures sprayed by lidocaine 2% in groups B and C?

Reply: Thanks for the comment. As demonstrated in the figures below, lidocaine in group B was delivered to Murphy hole by a single channel tube. As lidocaine was sprayed out through one big hole on the wall of catheter, it may not be evenly dispersed. The structure that got sprayed was basically the wall of respiratory tract through which the catheter passed during intubation to achieve intratracheal surface anesthesia.

As for group C, lidocaine was applied through a two channel system. Half dosage of lidocaine was sprayed on the tracheal wall through the small holes at the lower end immediately before intubation, while the other half of dosage was applied 5 seconds after intubation through the small holes at the upper end. The structure that got sprayed was similar to that in group B; however, the drug was dispersed more evenly and would be better maintained on the tracheal wall that need it the most.

9. Page 9 and line 197: Change 'T2 to T1' to 'T2 to T3'.

Reply: Thanks for the kind correction. We apologize for the typo. Correction has been made in the revised manuscript.


Reply: Sorry for the ambiguity. Changes (as highlighted in revised manuscript) have been made to better clarify our point.

11. In the discussion, the manuscript has to admit that the hemodynamic and other differences between group B and C are small and may not be clinically important albeit they are statistically significant.

Reply: Thanks for the comment. We have added the following information in the revised manuscript (as highlighted in manuscript): We further analyzed whether the effect was attributable to lidocaine itself or to the modified approach of administration by comparing the parameters between the groups B and C. The SBP (T4), angiotensin II (T2, T3, T4), and blood sugar (T4) in Group C were significantly lower than that in Group B. Similarly, the trend of change from T1 to T4 showed more gradual fluctuation in group C than in group B. Therefore, these results suggested that the modified intratracheal drug delivery catheter can improve airway-circulatory reflexes. However, the limited sample size of our study should be considered while
interpreting our results: despite the statistically significant analysis results, whether the
differences between group B and C are clinically important should be further studied.

Associate Editor: I am satisfied with Replies to comment 8 to 11