Author’s response to reviews

Title: Comparison of Supreme laryngeal mask airway versus endotracheal intubation for airway management during general anesthesia for cesarean section: a randomized controlled trial

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16 May 2019

To: Dr Guangde Tu
The Editor
BMC Anesthesiology
Dear Dr Tu,

RE: “Comparison of Supreme laryngeal mask airway versus endotracheal intubation for airway management during general anesthesia for Cesarean section: a randomized controlled trial” (Submission ID: BANE-D-19-00030R1)

Thank you very much for the review of our manuscript entitled "Comparison of Supreme laryngeal mask airway versus endotracheal intubation for airway management during general anesthesia for Cesarean section: a randomized controlled trial" (Submission ID: BANE-D-19-00030R1).

We appreciate your comments and kind help to improve on the manuscript.

Please find below point-by-point responses to each of the comments (in Italic red font).

Editor’s comments:

Reviewer reports:

Warwick Ngan Kee (Reviewer 1): General Comments:

This is an interesting study that compared the use of the Supreme Laryngeal Mask Airway (SLMA) versus endotracheal intubation (ETT) in patients having general anesthesia for elective caesarean delivery. The use of supraglottic airways for caesarean delivery is an area of current controversy so the study addressed an area that is very clinically relevant. The study appears to have been well conducted and the manuscript is well presented. My main concerns relate to the statistical methods used and the interpretation of the results. I will offer my opinion below but I would recommend consultation with a statistician to confirm.

------ Thank you very much for your time and effort to review our manuscript.
The study used an equivalence design which may not be appropriate when considering the conclusion that the SLMA is an acceptable alternative airway to ETT. The equivalency design was based on determining whether first insertion rate for ETT was within the equivalence boundary centered on first success estimate for SLMA. As I see it, this is incorrect; the equivalence boundary should be based on the estimated success rate for ETT. However, given that the failure rate for ETT is very small (0.4%, reference #2) I would expect a much larger sample size would be required. Additionally, I do not understand why an equivalence design was chosen. Given that ETT is the accepted standard, a non-inferiority design may be more appropriate. This would also need to be based on the estimated success rate for ETT so the corresponding sample size again would need to be very large.

The implication of the above is that even though this was a relatively large study, it may still be underpowered for the primary outcome.

------ Thank you for your thoughtful comments. A non-inferiority design was a viable alternative design for our trial but an equivalence design was, and is, more appropriate due to the following:

1) First, our primary endpoint, first-attempt success rate, is a subset of success rate (i.e. failure rate = 1 – success rate) and as such the ETT rate of unsuccessful first-attempts was expected to be higher than 0.4%. This is supported by a retrospective study of the performance of video laryngoscopy in an obstetric unit (Aziz M. et al. 2012), that reported 96.3% first attempt success rate of direct laryngoscopy. Also, Kim et al 2013 reported 80% overall first attempt success rate of ETT in an emergency department.


2) Second, it was not evident that ETT is superior to SLMA, as our previous study showed an SLMA first-attempt success rate of 98% - slightly higher than the ETT first attempt success rates.

3) Third, SLMA was, and still is, considered the standard of care at the study centre. Estimates of first attempt success rate from our previous SLMA studies were conducted in this centre and hence SLMA was used as the reference technique for this study as it reflected the standard of care in our study centre. Therefore, an equivalence trial design with the objective to demonstrate that SLMA and ETT had no clinically meaningful difference (i.e. they are clinically equivalent) seemed more appropriate given the high first attempt success rate (98%) in our previous study. Also, we calculated the sample size based on SLMA first attempt success rates as it was the standard of care in our centre.

Specific Comments:

Background.

This is very long. I would recommend reducing the length and focusing on the main issues and justification of the study. Much of the commentary can be deleted or moved to the Discussion.

------ We have revised the Background. Please refer to the revised manuscript with track changes.
Methods:

P8L14. It is very interesting that the SLMA is the routine method of airway management for GA caesarean delivery at the hospital. It may be useful to add a comment how long and for what reason.

------ SLMA is the routine method of airway management for Caesarean delivery, and has been so for more than a decade. This technique avoids potentially difficult laryngoscopy and provides good training for supraglottic airway management at the study centre. Also, parturients have relatively lower body mass index at the study centre.

P8L34. The study was conducted from 2013-2014. Why has it taken so long to submit?

------ Prior to this submission, the manuscript was submitted to other journals, and we took the time to improve the article based on the comments by other reviewers.

P9L2. Please give more details on cricoid pressure here. Who performed it and how was it standardized?

------ Cricoid pressure was performed by subspecialty nurses who were specially trained to assist the anaesthetists in clinical practice. This has been indicated in Methods, page 9. As part of their routine training, they were instructed to apply cricoid pressure consistently. They were also briefed about the study and the need for consistent cricoid pressure. However, we acknowledge the lack of direct measurement of cricoid pressure applied, and have mentioned the following in the Discussion, Page 18: “Finally, cricoid pressure was applied by the anesthetic nurses, who were briefed on the study and the need for consistency. They applied cricoid pressure according to routine hospital practice, but cricoid pressure was not directly measured.”

P9L2. Why was a range of propofol from 2-3 mg/kg used? Please specify in results whether there was any difference in propofol dose between groups.

------ We specified the range of acceptable doses for Propofol in our study protocol to standardize the dose given to both groups. However, the exact doses given was not recorded.
P9. Please specify the head position and type of pillow.

----- The pillow used are the routine pillows used at the hospital and patients were put in the “sniffing the morning air” head position.

P10. The criteria for successful placement for ETT do not seem to be as well defined as for SLMA. In particular, was a 60s time limit imposed for ETT and what was done if this was exceeded? I would recommend basing the analysis on success within the same time limit for both groups.

----- Thank you for your comment. The criteria for ETT success was exactly the same as in SLMA, with respect to the requirement for auscultation, capnography, orogastric tube positioning, and cuff pressure. The above have been described in the Methods, page 11: “For all parturients, successful placement of the airway device was confirmed by auscultation and the presence of end-tidal carbon dioxide on the capnogram.”

It was important for us to define the criteria for SLMA failure (>2 attempts, >60 seconds, or desaturation), as there is a paucity of guidelines for failed SLMA insertion in obstetrics. Conversely, the response to failed ETT insertion is guided by the OAA-DAS guidelines which the anaesthetists adhere to in the event of failed intubation.

P11L39. The obstetricians were requested to reduce fundal pressure during delivery. Is this standard practice. This has important implications for the external validity of the findings.

----- This is standard institutional practice. Furthermore, the obstetricians were reminded to reduce fundal pressure uniformly for all cases. This was mentioned in the Methods, page 11.

Results:

P14L29-32. Please include actual data for success rates.

----- Thank you. We have added the actual data to the results section.
P14L44. "we felt that this might not be clinically relevant". Subjective comments should not be included in Results. Please move to Discussion.

----- Thank you. We have removed the statement from Results.

Discussion:

P18L19-22. "the current practice of endotracheal intubation for Caesarean section should still be advocated…” This seems to contradict the stated routine practice by the authors of using SLMA.

----- The standard of care for most institutions is endotracheal intubation. As the concerns of aspiration was not adequately powered, it would be difficult to advocate the use of SLMA for routine practice in this study. Nonetheless, our data does suggested that the risk-benefit ratio of SLMA use should be considered in specific cases where minimizing time to ventilation and securing airway are important. The objective of our study was to demonstrate that SLMA and ETT had no clinically meaningful difference. Therefore, for routine care, we still advocate the continued use of endotracheal intubation.

Ron George (Reviewer 2): Thank you for submitting your manuscript to the BMC Anesthesiology and giving me the opportunity to read and critique your article - Comparison of supreme laryngeal mask airway versus endotracheal intubation for airway management during general anesthesia for cesarean section - I hope you will find these comments useful in revising your manuscript.

----- Thank you very much for your time and effort to review our manuscript.
1. This is a very well written article, however I feel you should provide readers with a greater reasoning of the equipoise of why this should be done. I sense this is more of a non-inferiority study and should be possible described as such. I cannot imagine thinking that you suspected SLMA could improve first attempt success as the ETT rate is so high.

------ Thank you for your thoughtful comments. A non-inferiority design was a viable alternative design for our trial but an equivalence design was, and is, more appropriate due to the following:

1) First, our primary endpoint, first-attempt success rate, is a subset of success rate (i.e. failure rate = 1 – success rate) and as such the ETT rate of unsuccessful first-attempts was expected to be higher than 0.4%. This is supported by a retrospective study of the performance of video laryngoscopy in an obstetric unit (Aziz M. et al. 2012) that reported 96.3% first attempt success rate of direct laryngoscopy. Also, Kim et al 2013 reported 80% overall first attempt success rate of ETT in an emergency department.


2) Second, it was not evident that ETT is superior to SLMA, as our previous study showed an SLMA first-attempt success rate of 98% - slightly higher than the ETT first attempt success rates.

Therefore, an equivalence trial design with the objective to demonstrate that SLMA and ETT had no clinically meaningful difference (i.e. they are clinically equivalent) seemed more appropriate given the high first attempt success rate (98%) in our previous study.
2. Within the background (page 7 Line 7) you describe the reasoning why LMA use may be safe as the optimization of care that have altered the aspiration rates. To balance this argument you should highlight rising rates of women living with obesity and how ETT still may be the gold standard in many populations.

------ Thank you. The following sentence has been added in Background, page 7 “…factors that may enhance the margin of safety in this respect. However, rising rates of obesity and other risk factors for pulmonary aspiration may necessitate endotracheal intubation as standard of care.”

3. Why is the rate of GA for CS so high. This project is of marginal gain to women having a cesarean delivery and more gain may occur if the rate of GA wasn't so high at your institution.

------ The high incidence of GA for LSCS is largely due to patients’ request at our study centre. Many patients have expressed concerns regarding chronic backache and other potential complications of spinal anaesthesia.

4. Is RSI the correct term (page 9 line 1) as you are not intubating the trachea in one cohort?

------ Although we did not perform endotracheal intubation, the specific technique of rapid induction of anaesthesia and paralysis was similar in both groups. In the text, we specifically used the term “rapid sequence induction” instead of “rapid sequence intubation” to show that we were referring to the induction technique, not the method of securing the airway.

5. Was there block randomization? With such a large group I was surprised to see an identical number of subjects in each group with no loss of follow-up or withdrawals.

------ No. Simple randomization was employed. The identical number of subjects in each group was not unexpected given that none of the study participants was lost to follow-up and there were no early discontinuation from the study i.e. all randomized subjects completed the study.
6. The statistical significant difference in ventilation has a very narrow confidence interval. This lack of variation is quite remarkable and signals to me a specific technique issue that is used for SLMA that equates to this repeated difference. This is likely due to your large experience with this device and in this population. This warrants comment and discussion….I cannot think of a specific thing that would make my LMA insertion consistently 23 seconds faster. Please refine your discussion to ensure readers consider the statistical significance but perhaps limited clinical significance (page 16 line 10).

------ Thank you for your comment. We agree that the said confidence interval is narrow, which may be attributed to the uniformity in technique and ‘large’ sample size. The uniformity in technique may be explained by the fact that all airway maneuvers were performed by only three very experienced anaesthetists.

In our discussion, we highlighted that the use of SLMA may be advantageous as a rescue airway, partly because the shorter time needed for insertion may prevent potential hypoxia. This was mentioned in page 19, line 4.

7. Page 15 line 1 - in the results section please clearly define what you refer to as hemodynamic alternations.

------ We mentioned that there were lower heart rate and systolic blood pressure during the airway insertion period for SLMA compared to ETT (page 15, line 2). Relevant results are provided in Table 2.

Research Square (Reviewer 3): "STATISTICAL REVIEWER ASSESSMENT:

Is the study design appropriate for the research question (considering whether the analyzed population accurately reflects the design and whether you see any problems with control/comparison groups, e.g., likely confounders)?

Yes - overall design, population, and control groups are appropriate

------ Thank you for your comments.
Are methodologies adequate and well implemented (considering whether assumptions are addressed and whether analyses are robust)?

Yes - methodologies are adequate and well implemented, assumptions are addressed, analysis is robust

------ Thank you for your comments.

Are the analyses adequately communicated (considering whether reporting details are adequate and whether figures and tables are well labeled and described)?

No - there are minor issues

------ We have addressed the queries from other statistical related questions.

Does the interpretation accurately reflect the analyses without overstatement (considering whether limitations/bias are acknowledged and whether accurate descriptors, e.g., 'significant', are used)?

Yes - interpretation accurately reflects analyses, limitations/bias are acknowledged, accurate descriptors are used

------ Thank you for your comments.

Could an appropriately REVISED version of this work represent a statistically sound contribution?

Probably - with minor revisions

------ Thank you for your comments, we have done the minor revisions.
STATISTICAL REVIEWER COMMENTS: The authors conducted an equivalence study to compare Supreme laryngeal mask airway and endotracheal intubation. The study is well powered (460 patients per group). The flow chart is helpful. All tables were easy to understand.

------ Thank you very much for your time and effort to review our manuscript.

REQUESTED REVISIONS: The authors did a good job overall. It might be a good idea to state their hypothesis at the end of introduction (page 7). What is their hypothesis when they design this study? For the results section, they compare SLMA with ETT (ETT as the reference). This is true for Table 2. However, they switched to the compare of ETT with SLMA (SLMA as the reference). You can clearly tell by the risk ratio of presence of blood on airway devices. It might be a good idea to be consistent. They need to double check on the accuracy of the risk ratio. Take the presence of blood on airway devices (Table 3) as an example, the risk ratio should be 1.28 (if I compare ETT with SLMA). I have a hard time understanding where the RR=1.31 comes from. Please make sure that you use ETT as the reference in Table 3."

------ Thank you for your comment. We have adjusted the tables and manuscript such that the reference (SLMA) is consistent, and utilized odds ratio instead of RR.