Author’s response to reviews

Title: The oculocardiac reflex and depth of anesthesia measured by brain wave

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BANE-D-18-00420
The oculocardiac reflex and depth of anesthesia measured by brain wave
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BMC Anesthesiology

Your manuscript "The oculocardiac reflex and depth of anesthesia measured by brain wave" (BANE-D-18-00420) has been assessed by our reviewers. Based on these reports, and my own assessment as Editor, I am pleased to inform you that it is potentially acceptable for publication in BMC Anesthesiology, once you have carried out some essential revisions suggested by our reviewers.

Point Question Response
A-1 Hyun Jin Shin (Reviewer 1): The oculocardiac reflex is a decreased heart rate in response to stimulation of the eye or the ocular adnexa. The oculocardiac reflex occurs most often during strabismus surgery. Thyroid-associated ophthalmopathy, myasthenia gravis, cardiac disease, a light level of anesthesia, the consumption of certain narcotics, and the age of the patient have been identified as predisposing risk factors for a catastrophic oculocardiac reflex. This study was designed to examine the effects of depth of inhalational anesthesia monitored BIS on the OCR. The manuscript is generally well written and the methodology was appropriate. The results of present different from previous studies reporting deeper inhalational anesthesia monitored by BIS protects against OCR. However, present study is worth being accepted because it has provided the large amount of data and statistical methods reported in this study was quite reasonable. Thank you. We aimed to employ identical extraocular muscle afferent stimulus to a large number of patients- differing from other authors methodology.
B-1 OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)?
No - there are minor issues  We have clarified the primary outcome and reasons our study differs from prior investigations. We identify the uniformity of our OCR elicitation over more than 2 decades.

B-2 DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?
No - there are minor issues  We highlight the intra-subject control aspect and carefully-defined method uniformly eliciting oculocardiac reflex for all patients. The multiple variable correlation of continuous variables increases power of comparison and we also report as OCR > 20%. We now more carefully identify confounders and our attempts to identify and reduce bias.

B-3 EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results?
No - there are minor issues  Unfortunately our two surgery centers did not purchase the same type of brain wave monitor; we tried to keep our groups separated in case the type of monitor influenced results.

B-4 Statistics - Is the use of statistics in the manuscript appropriate?
No - there are issues with the statistics in the study  We looked at many factors and employed multiple variable analysis of continuous variables to retain statistical power. Additional study of

B-5 INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?
Yes - the author's interpretation is reasonable  Thank you. We tried to keep our conclusions within the scope of our sample size.

B-6 GENERAL COMMENTS: The study is interesting especially because of the large number of patients included. The authors present a well structured approach.  Thank you. Since profound oculocardiac reflex is rare, we have aimed to utilize identical stimuli over large numbers of elective strabismus surgery patients in different surgery centers.

B-7 However, relevant prior studies are not mentioned (e.g. Medicine (Baltimore). 2015 May;94(18):e807; Medicine (Baltimore). 2015 Feb;94(5):e484). These excellent summary papers are now referenced early in the introduction, in methods and in conclusion with one additional paper also included (Meuwly C, Chowdhury T, Sandu N, Golanov E, Erne P, Rosemann T, Schaller B: Definition and Diagnosis of the Trigeminocardiac Reflex: A Grounded Theory Approach for an Update. Front Neurol 2017, 8:533.)

B-8 Also relevant findings linked in Fig 2 (age-dependence) are not further evaluated  We have clarified sedative and opioid use by cohort in Table 1 and how the younger children may have had more sedatives pre-operatively.

B-9 REQUESTED REVISIONS:
The research hypothesis should be more clearly defined and explain specifically what gap in the literature should be closed by the research. This would help to better align with the conclusion.

    Changed end of introduction to: “Both anesthesia and surgeon have an influence on OCR. Depth of anesthesia is impacted by several components including inhalational agent concentration, nitrous oxide, opioids, propofol, sedatives, etc. OCR is also markedly influenced by the duration, form
and amount of tension[3, 4, 14] on different extraocular muscles that were not controlled in former papers. We hypothesized that, over a range of anesthesia depths monitored by two different brain wave devices, we would find a correlation between specifically controlled oculocardiac reflex and lighter anesthesia.”

B-10 What are the patient’s characteristics? We added Table 1 with demographic and other cohort comparisons.

B-11 There is a need to cite other important works on the TCR of the field and to make a balanced reference selection. Three TCR references are now included.

B-12 ADDITIONAL REQUESTS/SUGGESTIONS:
It should be mentioned to avoid biases/confounders. Additional details included in METHODS: “There was no health or age related bias directing patients to either surgery center, however younger patients were more likely to receive pre-operative sedation- that may serve as a confounder with respect to age. Anesthesia staff was equally likely to increase or decrease anesthesia depth over the course off the surgery. The known confounder dexmedetomidine was not used in this study group. “ Issues of confounders detailed in the conclusions now.

Our changes can be found in dark red print on the manuscript.