Author’s response to reviews

Title: Comparison of the effect of different infusion rates of sufentanil on surgical stress index during cranial pinning in children under general anaesthesia: a randomized controlled study

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Author’s response to reviews:

Reviewer reports:

General comment:

1. Though the manuscript is certainly legible, it could improve from the input of an English native speaker. Especially some sentences in the results, as well as the discussion seem a bit awkward (forgive me here.....I do not speak a word of Korean, so I certainly do not judge you here): i.e. "Calculated SSI assessment during cranial pinning of head fixation did not exhibit the differences among the groups."

Response) Thank you for your advice. This manuscript has been corrected by a native speaker and we have attached the certification of proof.

2. You call the method SSI. This term was abandoned by GE many years ago and it was since re-branded into "surgical pleth index [SPI]". Is the manuscript so old, or why do you use SSI?

Response) We appreciate your recommendation. Unfortunately, we do not have a GE monitor; therefore, we have used SSI, instead of SPI, because the algorithm to calculate SSI is the same as the algorithm to calculate SPI. Therefore, we are simply distinguishing our method for obtaining
data. It is likely that readers are aware of the equivalence between SSI and SPI. However, if the reviewer recommends that we use SPI instead of SSI, we can change this in the manuscript. We want to emphasize that this might not be technically appropriate.

Abstract:

1. Please describe the time course of BP and HR after the pinning in a little more detail. Focus on the issue of whether or not these parameters actually changed as a result of pinning.

Response) The sentence was revised in the Methods section as recommended by the reviewer.

Methods:

1. Though it appears that you did not include many very young children, you describe the method of induction of anaesthesia in this group. These kids (< 3 yrs.) apparently received atropine on induction! Atropine, as well as many other substances (i.e. phenylephrine, metaraminol, catecholamines, glycopyrrolate, etc.) are well know to significantly change heart rate variability (one of the underlying parameters in calculation of SPI). Hence, they MUST BE EXCLUDED! Please elaborate, if/how many patients received any of the above substances. These will need to be excluded!

Response) Thank you for your valuable recommendation. We must note that, in our institute, we administer atropine routinely for neurosurgical patients to prevent the bradycardia that is induced by opioid usage. Importantly, atropine was administered to all patients in this study to reduce bias within the sample. We have added this to our discussion of study limitations.

2. Please describe in detail which sensor you used for the oxygen saturation assessment in these children. Did you measure on the fingers or toes? Only a measurement with a finger sensor would be validated for SPI calculation!!!! So please describe this detail in the methods.

Response) We monitored peripheral oxygen saturation with a finger sensor.

3. I am not 100% sure whether I can follow the sample size calculation. Could you elaborate more on this? Its unusual for such a small sample size to achieve a power of 95% - are you sure about this? Why did you elect such a high power (vs. i.e. a more standard 80%)? Of note: its either the "University Kiel" or "Universitaet Kiel", not "Universitat Kiel".
Response) We apologize for the mistake. We have corrected that point and described our estimation of sample size in more detail.

4. Though you mention this in the discussion, but: could you please clearly describe how long the sufentanil infusions were running until the head pinning was performed? If the infusion was only started at the time of intubation, I would assume that only a few minutes passed until the surgeon would have liked to pin the head. This may not be sufficiently long to achieve a steady state in each group. Hence it could be that there was no difference for the sufentanil concentration between the groups. Please provide some pharmacokinetic modelling to indicate how long such infusion likely needed to run to assume a steady state. I understand that you did not test blood concentrations....but one would need to know whether there was even a chance for differences to establish between the groups.

Response) The minimum sufentanil infusion time was at least 1 hour. Additionally, we simulated the estimated sufentanil concentration after continuous infusion, using Guay’s model, and found that all three infusion rates reached steady-state between Cp and Ce concentration within 45 minutes. We added this point to the discussion.

Results:

1. I note that the data is generally displayed as median (IQR)...but for comparison of the "reaction" to pinning ANOVA was used? I assume that the data did not follow normal distribution? Why did you not use a non-parametric test instead? Would the outcome have been different?

Response) Thank you for your recommendation. We analysed the data with RM ANOVA because this method is robust. (Reference; http://www.ats.ucla.edu/stat/sas/library/repeated_ut.htm, https://statistics.laerd.com/spss-tutorials/two-way-repeated-measures-anova-using-spss-statistics.php) However, we reanalysed the data with a different method as recommended by the reviewer and found no differences among the three groups over the time. Further, we performed an additional analysis of changes in SSI, BP and HR within the same group over time; these results were added to the text.

2. The table displaying the BP results should not have the P values in the actual table (better just * and P values in footnote). To me it looks very much as if the BP values at point 2 and 3 may
have also been different to baseline. But no indication of this is provided. Were these indeed different?

Response) We analysed the data with a different method and found different results; this was changed in the text. Thank you for your recommendation.

3. The table with the HR results does lack any p values at all. In the text the authors describe some vague difference within the HR groups.....but it does not show. I would prefer if each table could have a footnote indicating i.e. "no differences found between time points and between sufentanil groups", or similar. Or indicate with a symbol in the table where significant difference were found.

Response) Thank you for your kind advice. We have corrected the mistake.

4. I do not like the figure with the SPI values, as it lacks any idea about the distribution/spread of data. Could you not display this in a table similar to your HR and BP tables?

Response) Thank you for your recommendation. The figure was deleted and replaced by a table.

5. Ideally, I would like to see a result for SPI vs HR and BP (all suf. groups combined and for each single group L,M,H) indicating whether or not the parameters changes with head pinning?

Response) Statistical analysis was performed as recommended by the reviewer; SPI did not show a difference over time. (please see graphs below)

Discussion:

I miss a discussion about whether or not SPI, HR and BP at all reacted to head pinning. Maybe its there....but its too vague for me to really understand this well. I would like to see this being discussed, and then, subsequently, whether or not inter-group differences were found.

Response) A more detailed treatment of this topic was written in the Discussion section.
To me it looks like there may have been no differences between the sufentanil groups for any parameter. The latter could be based on the fact that probably no differences in sufentanil were actually established (see my comment above).

Response) You are correct that there were no differences among the three groups over time, within any parameters. Some within-groups parameters exhibited changes after pinning; this point was described in the text.

Also, in relation to my comment about atropine et al.: you will need to discuss this issue.

Response) Please note that this question was addressed above; we added this into the Discussion section and into the listing of limitations in this study.

Reviewer 2.

ABSTRACT:

Background: Suggest revision of first sentence. "Surgical stress index (SSI) is a known monitor of intraoperative nociception"

Response) Thank you for your advice. We have revised the sentence as recommended.

-Third sentence, suggestion for revision: "We investigated the effect of different infusion rates of sufentanil on SSI during pinning in children under general anesthesia"

Response) The third sentence was revised as the reviewer recommended.

Methods:

-The mcg/kg/hour did not come through as a proper symbol.

Response) The unit was corrected.

-Suggestion for revision: "Forty-nine children (2-12 years of age) were enrolled for neurosurgery with pinning."

Response) The sentence was revised as the reviewer recommended.
BACKGROUND

-Lines 10-11: Suggest revision to: "Therefore, maintenance of the balance between nociception and antinociception is important during anesthesia"
Response) The sentence was revised as the reviewer recommended.

-Line 16: Suggest revision to: "However, the reliability of these responses is variable due to potential confounders"
Response) The sentence was revised as the reviewer recommended.

-Lines 21-22: Should all of these be capitalized? Example: Analgesia Nociception Index? Some are capitalized and some are not. Please double check ‘
Response) The sentence was revised as the reviewer recommended.

-Line 46: suggest revision to "and the infusion rate is typically adjusted according to blood pressure…”
Response) The sentence was revised as the reviewer recommended.

-Line 47: suggest revision to: "However, BP and HR may not be valid because…”
Response) The sentence was revised as the reviewer recommended.

Final line in background: revise as was suggested for abstract.
Response) The sentence was revised as the reviewer recommended.

METHODS

-Page 4, line 28: revise to "An equal number of patients…”
Response) The sentence was revised as the reviewer recommended.
The authors state that each patient was "adequately hydrated". What does this mean? It needs to be explained to ensure that readers understand what was done to ensure euvo leukemia

Response) In our hospital, preoperative hydration is performed according to the Holliday-Segar guidelines during the fasting period. Further, initial vital signs were checked and found to be within acceptable ranges. Thus, we were sure that the recruited children were clinically euvoelamic. We have added this in the Methods section.

Page 5, line 43: revise to "Anesthesia was induced with atropine (0.02 mg*kg-1, 0.5 mg maximal dose) and sodium thiopental…"

Response) The sentence was revised as the reviewer recommended.

Please explain why atropine was given and how it was ensured that this did not confound results.

Response) In our institute, atropine is routinely administered to prevent the bradycardia that is induced by opioid administration, thus reducing the secretions. Additionally, we administered atropine to all patients to minimize bias within the data.

Why were investigators not blinded to the infusion rate? Was this considered?

Response) Practically, it would not have been easy to blind the investigators because one of them was the attending anaesthesiologist during the surgeries. As the infusion rate did not change during the study, the study may not have been biased even though the attending anaesthesiologist was not blinded. Importantly, the staff that performed analyses were blinded to each patient’s assigned group and all data were automatically obtained via computer.

The investigators state that pinning was performed "at least one hour following the start of sufentanil administration". Were there patients that received sufentanil for significantly longer than one hour? This should be stated.

Response) Most procedures were standardized neurosurgical procedures; thus, all patients received sufentanil for at least 1 hour immediately prior to pinning.
How was sevoflurane vs. desflurane selected? How many patients received des vs. sevo? Can the authors know for sure that this was not a confounder?

Response) Desflurane was used in seven, six, and seven patients in each of the three groups. We monitored BIS for all patients; this might provide almost the same depth of anaesthesia in each patient. The selection of inhalational anaesthetics was chosen by the attending anaesthesiologist, as described in Table 1 in the text.


Response) This means that SSI was calculated after obtaining the data; this was clarified within the text.

Page 6, line 5: Suggest revise to: "The differences in the primary and secondary outcomes between the groups were evaluated using ANOVA for repeated measures."

Response) The sentence was revised as the reviewer recommended.

RESULTS

-The authors state that there are "no differences among the three groups" in terms of demographic characteristics, but no statistical testing was performed. I don't think you can say there were no differences if you don't run statistics.

Response) We performed new statistical analyses and described them in the Methods section.

DISCUSSION

Page 8, line 5: I would replace "painful" with "stimulating…as the authors state earlier in the manuscript, there is a difference between nociception and pain

Response) The sentence was revised as the reviewer recommended.

Page 8, line 19: same comment as above

Response) The sentence was revised as the reviewer recommended.
Page 8, line 32: "…for nociception response during anesthesia and hypothesized." I think there is something missing from the end of this sentence.

Response) We have corrected this sentence.

Page 8, line 34: suggest revision to: "However, we found no differences in SSI values despite differing infusion rates of sufentanil in contrast to the previous study."

Response) The sentence was revised as the reviewer recommended.

Page 8, line 43: suggest revision to: "Therefore, SSI measurements and traditional clinical findings exhibited quite disparate results." The study is not designed to measure outcomes.

Response) The sentence was revised as the reviewer recommended.

Page 8, line 52: suggest revision to: "The BP changes seen in this study may explain the lack of differences seen in SSI."

Response) The sentence was revised as the reviewer recommended.

Where a mandatory Declarations section is not relevant to your study design or article type, please write "Not applicable" in these sections.

Response) The section was changed.

For the 'Availability of data and materials' section, please provide information about where the data supporting your findings can be found. We encourage authors to deposit their datasets in publicly available repositories (where available and appropriate), or to be presented within the manuscript and/or additional supporting files. Please note that identifying/confidential patient data should not be shared. Authors who do not wish to share their data must confirm this under this sub-heading and also provide their reasons. For further guidance on how to format this section, please refer to BioMed Central's editorial policies page (see links below).

Response) The section was changed.
Declarations

- Ethics approval and consent to participate
- Consent to publish
- Availability of data and materials
- Competing interests
- Funding
- Authors' Contributions
- Acknowledgements