Author’s response to reviews

Title: Intraoperative cerebral oxygen saturation trend of values and its relationship with cognitive decline after total knee replacement

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Version: 4
Date: 7 April 2014

Author’s response to reviews: see over
Reviewer's report

Title: Intraoperative cerebral oxygen saturation trend of values and its relationship with cognitive decline after total knee replacement

Version: 2  Date: 10 February 2014

Reviewer: Marcin Wasowicz

Reviewer's report:
Authors of the study entitled: “Intraoperative cerebral oxygen saturation trend of values and its relationship with cognitive decline after total knee replacement.” Conducted post hoc analysis of previously published data (Acta Anaesthesiologica Scandinavica). They hypothesized that decline of regional cerebral saturation has an association with post-operative decline. Authors should be complemented for conducting a battery of difficult psychosomatic test but unfortunately study has serious flaws. It is hard to believe that this one factor will have influence on such a serious complications.

Answer:
Dear Sir, there are published studies dealing with the subject of cerebral oxygen saturation values and postoperative cognitive dysfunction. We are not the first ones in making such an association, for instance:


Reviewer: There is no data in the manuscript on following, common postoperative factors, which can contribute to described findings:

1. Incidence of post-operative delirium

Answer:
Any patient in our study was diagnosed of postoperative delirium

2. Incidence of intra- and post-operative hypotension

Answer:
There was no clinically relevant hypotension since patients were continuously monitored and they were treated with vasoactive drugs as soon as a minimal hypotension was shown. Thus it is not possible that hypotension might play a role of bias or confounding in the cognitive assessments. However, to rule out any concern from the reviewer, we have now included the number (%) of patients treated with vasoactive drugs (atropine/ephedrine) in table 3. Please note that there seem to be no role of those drugs on the cognitive assessments.

In our previous study hemodynamic variables did not emerge as risk factors for POCD at day 4th or at 3 months.
3. Incidence and severity of peri-operative anemia

**Answer:**
The minimum peri-operative Hb is now included in table 3 in addition to the discharge Hb, Blood loss (% of total volume) and the number (%) of transfused patients. Please note that the current data do not support the hypothesis that lower Hb levels are correlated to an increased incidence of the different types of cognitive impairments. Thus, this cannot be considered a potential source of bias in the line suggested by the reviewer.

**Reviewer:** It is impossible to formulate meaningful conclusions without aforementioned data being included in the analysis. If study is to be considered for publications, it will need significant revision and inclusion of proposed data.

**Answer:**
We thank the reviewer for the valuable comments in the interest of the manuscript improvement. We think that the answers to the raised concerns have been properly addressed, and changes in the manuscript have been done (Table 3).

**Reviewer:** Detailed comments:
- Please define psychopathology

**Answer:** Psychopathology is a synonymous of psychological state dysfunction. It includes from psychiatric disorders to mood alterations (anxiety-depression). All these were evaluated with our battery of test. In this study we mean by psychological state dysfunction the mild-moderate changes in mood state/emotional instability, including subjective complaints evaluated with the specific scores detailed in the Appendix. We have substituted this word along the manuscript in order to avoid confusion.

- Lack of inclusion/exclusion criteria

**Answer:** We did not include it because it is a “post hoc study” and this information is in the first published study. We add this information to our manuscript as the reviewer suggests. “All patients over the age of 65 years, ASA 1–2, scheduled for total knee replacement were considered candidates for enrollment, subject to the following exclusion criteria: a history of central nervous system disorder or previous neurosurgery or the use of medications affecting the central nervous system (tranquilizers, antidepressants, etc.)”.

- What about baseline data?
Based on North American practice it is hard to believe that patients who are coming for total knee replacement and being over 65 are predominantly ASA 1 or 2.

**Answer:** We designed our study for a homogeneous population undergoing a single type of surgery, enrolling a smaller number of patients with similar characteristics and in relatively good health (ASA 1–2). All lived in the same metropolitan area, were operated on early in the morning to control for circadian rhythms, and received the same type of anesthesia and post-operative analgesia. 60% of patients had arterial
hypertension under control; 10% were diabetics; 5% had asymptomatic coronary artery disease; 3% atrial fibrillation treated and with a controlled heart rate frequency; 2% stable asthma and 29% obese (no morbid obesity).

- Keep your discussion simple

- Your main finding
- How does it compare to the other, similar studies
- Limitations
- Conclusions

**Answer:**

*We have added some sentences to our discussion in order to clarify the main finding and the limitations.*

*In our opinion now contains all the topics suggested by the reviewer.*
Reviewer's report

Title: Intraoperative cerebral oxygen saturation trend of values and its relationship with cognitive decline after total knee replacement

Version: 2

Date: 23 January 2014

Reviewer: Matthias Heringlake

Reviewer's report:

The present study entitled “Intraoperative cerebral oxygen saturation trend of values and its relationship with cognitive decline after total knee replacement” by Dr. Salazar and colleagues aims to determine the association between perioperative changes in cerebral oxygenation and postoperative cognitive decline (POCD) in orthopedic patients. This is a retrospective analysis of patients primarily enrolled in a trial analysing the effects of perioperative warming on cognitive dysfunction.

General comments:

The authors have to be congratulated for investigating the association between cerebral desaturation in a population of patients undergoing regional anesthesia, i.e. in patients that were awake during surgery. This approach is clearly different to most other studies analysing the association between the time course of cerebral oxygen saturation (ScO2) and POCD.

As the primary finding of the present study the authors observed that a left to right ScO2 difference may be associated with a postoperative decline in memory function. Again, this is an unique finding, since most other studies have largely ignored differences in ScO2 between hemispheres and have focussed on the mean or maximum of ScO2 desaturation, independent from side differences.

Major Compulsory Revisions:

1. Based on the findings of the primary study, perioperative warming may lead to a significant increase in POCD. Since the mechanism by which cerebral hyperthermia leads to POCD may include other factors than changes in cerebral oxygenation (i.e. increased cerebral inflammation; an issue supported by the trend towards higher CRP levels in patients with POCD in the present manuscript) I feel that the analyses need to be adjusted for the primary group assignment.

Answer:

Please find in the table below the univariate raw analysis and the randomised-group (warmed vs standard treatment) adjusted risks [95%CI] estimates using logistic regression models. Of note, both the Ratio R/L and the Mean Difference remain as independent predictors with no relevant changes in the risks estimates while the effect of the randomised group is clearly well away from the statistically significance.
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<th>Univariate Analysis</th>
<th>Adjusted</th>
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<td>Ratio or Mean Difference</td>
<td>Ratio or Mean Difference</td>
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<td></td>
<td>OR [95%CI]</td>
<td>p-value</td>
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<tr>
<td>Ratio R/L</td>
<td>0.86</td>
<td>0.003</td>
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<tr>
<td>Mean Difference</td>
<td>0.81</td>
<td>0.005</td>
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Additionally, the reader needs to be informed more precisely about the objectives and results of the primary study (reference: 12).

**Answer:**
The objective of this post hoc study is different from the previous one. In our opinion the reader will not obtain useful information adding more data to the present manuscript.

2. The percentage of patients showing a reduction in a specific cognitive functions, i.e. the predefined groups, are rather small. Consequently is hard to imagine, that the respective differences in cerebral oxygen saturation in these small groups are robust if repeated prospectively. Thus it may be appropriate to additionally analyse the total group of patients with any kind of POCD in comparison with patients showing no cognitive decline, Otherwise the patterns in cerebral oxygenation – even if highly interesting - may be regarded as merely descriptive. Additionally, the reader might be especially interested to learn if the association between side differences in cerebral oxygen saturation is independently associated with POCD. This makes a logistic regression analysis including other factors potentially mediating POCD - mandatory

**Answer:**
The comment is very well taken and this point was extensively discussed in the planning stage with the Anaesthesiologists and Psychologists teams before the initiation of the analysis. However, it was considered that, a priori, the role of the predictors would likely be different and thus, an overall assessment would have the risk of mixing and overlapping variables and finally mask the predictors for each type of cognitive impairment.

3. Eight patients were excluded from analysis since they showed a combined POCD pattern. Even it is understandable with respect to the analysis of specific POCD patterns, it is difficult to understand why patients with a poor neurological outcome (i.e. those with more than one postoperative deficit) are excluded from the analyses.

**Answer:**
The objective was to identify potential predictors for net clinical presentations and this was the key justification for excluding those patients, please see also response to the previous questions for a discussion in this line. In addition to that, and as also highlighted by the reviewer, 8 cases represent a very small sample and this point...
together with the heterogeneity of that sample would likely lead to results difficult to be interpreted. Finally, we have had in mind the potential concerns of multiple testing, and despite this is an exploratory study for the planned objectives, we have tried to limit the number of analysis according to the plan and to avoid data-driven analysis.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I have received and continue to receive honoraria for lectures by Covidien, the manufacturer of the cerebral oxygen saturation monitor used in the present study.
Reviewer's report
Title: Intraoperative cerebral oxygen saturation trend of values and its relationship with cognitive decline after total knee replacement
Version: 2 Date: 17 January 2014
Reviewer: Thomas Hemmerling
Reviewer's report:
I have noticed that Table 1 is not complete with respect to the control group, pls complete all data....thank you

Answer:
We have no more date on control group. According to the reviewers comment we have made some changes in Table 1.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
'I declare that I have no competing interests'