Author’s response to reviews

Title: Effects of bupivacaine or levobupivacaine on cerebral oxygenation during spinal anesthesia in elderly patients undergoing orthopedic surgery for hip fracture. A randomized controlled trial

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Author’s response to reviews:

Dear Editor,

First of all we would like to thank your interest and your review of our manuscript. We consider all of your comments of great value and that they have been of great help to improve the manuscript. We hope that the new version incorporating all your suggestions can be considered for publication.

Below you will find our responses to all the comments raised. We have attached the modified manuscript with tracked changes an also a clean version.

Responses to reviewer reports:

Chin-Chen Chu, M.D., Ph.D. (Reviewer): Manuscript (Numbered BANE-D-18-00043 ) titled: Effects of bupivacaine or levobupivacaine on cerebral oxygenation during intradural anesthesia in elderly patients undergoing major orthopedic surgery for hip fracture, has been carefully reviewed. The authors conducted a perspective randomized study to compare the effect of intrathecal bupivacaine and levo-bupivacaine on regional brain oxygen saturation. Their results demonstrated no difference between the 2 group patients. The ideal is novel and the study was well designed and conducted. The strength of this study is the randomized clinical trial,
However, there are several ways in which the paper could be improved. Therefore, I suggest a major revision.

We appreciate your comments which have been very useful to improve the manuscript

1. Title:
   i. The term intradural is not common used in anesthesiology field, suggest replace with intrathecal or spinal, as you used in the manuscript. Besides, the wording major also seems unnecessary.

   We appreciate your comment. The title has been modified.

2. Abstract
   i. There was lack of report of data in this result section. At least, you need to report the data of your primary outcome between 2 groups, as you stated in the method section, i.e. the proportions of time of desaturation of these 2 groups and add a P value.

   ii. The secondary outcomes included neurological complications, this category is too broad. Suggest directly state what you have observed: disorientation, agitation or stroke symptoms, as stated in your text method section.

   iii. The abbreviation of neurological complication (NC) seems not necessary, because it only appeared 2 times, and you still use neurological complication in the result.

   iv. Conclusion: Suggest conclude your primary outcome first, followed by secondary outcomes.

   As suggested, the abstract has been reviewed and rewritten.

3. Background
   i. Line 24, suggest define the neurological complications you intended to observe.

   Cognitive status was measured by SPMSQ and any adverse event reported by the physician, related to nervous system was recorded. We have modified the sentence indicating how we measured cognitive status and changed neurological complications to nervous system adverse events.

4. Method
i. Design: line 5-12, just declare that you had Ethical Committee permission (the data and number) is enough.

This paragraph has been modified

ii. Line 41, it is not clear about the statement "..., related to severe cognitive decline". If your exclusion criteria were just based on the score. This statement only brought confusion to the readers.

You are right, this statement has been removed.

iii. The second page of method section, line 12-17, Only those converted to general anesthesia were dropped out? However, propofol and midazolam may also lower the blood pressure and decrease cerebral oxygenation. Especially, midazolam has an intermediate duration of sedation, and even lasted longer for geriatric patient. Whether the desaturation episodes happened during the sedation?

The objective of the study was to compare regional cerebral oxygenation, and secondarily, impact in cognitive status of elderly patients of using bupivacaine or levobupivacaine. Only patients in whom spinal anesthesia was not eventually performed were excluded. However patients who needed propofol or midazolam were included as they were still on spinal anesthesia and thus we decided to include them in the analysis, even if these drugs may alter blood pressure. The study was intended to be pragmatic, and thus any need of additional drugs to achieve anesthesia was recorded and taken into account.

iv. Why set the primary end point as the proportion of intra-operative time with desaturation, instead of the absolute time of desaturation? A longer operation time will thus dilute the proportion, I don't understand the rationale behind this. I think the AUC makes more sense than the proportion.

We chose as primary outcome the mean proportion of intra-operative time with regional cerebral desaturation defined as a rSCO2 relative reduction of 20% from baseline value. We also calculated the total time and the AUC which captures the time but also the depth of desaturation and would probably be what best describes the desaturation profile. However at the time of choosing one as primary endpoint mainly for sample size calculation we thought that the percentage of operative time with desaturation would be a variable with less dispersion and that would be valid for the comparison between groups.

v. The definitions of neurological complications were not clear. Who evaluated the neurological condition? The orthopedic surgeon or a neurologist? How do you define agitation? Besides, agitation is considered a psychological or neurological condition? Similarly, what is considered to be stroke symptoms? Clear neurological complications definitions and methods of measurement are important to this study because your main suggestion to readers was based on this. (see your conclusion)
Postoperative neurological consequences of regional anesthesia were evaluated by measurements of neurocognitive function with the SPMSQ. No other standardized measures for neurological complications were included in the protocol. However any adverse event reported by the responsible physician related to nervous system disorders according to the MEDDRA SOC were recorded, but the criteria to consider a neurological complication were not set a priori. The text has been modified to make it more understandable in this aspect.

All edits in this section of the manuscript have been implemented.

5. Results

i. Although, the grouping of patients was randomly assigned, it seemed that more patients in Bupivacaine group were ASA class 3. This may confound your analysis.

Despite random assignation of treatment group, there seems to be an imbalance in ASA. We think this imbalance has no impact on results as ASA was not a predictive factor for any of the study endpoints in the multivariate analysis. Moreover the disbalance is probably due to random, due to the small sample size, and not a real difference.

ii. Footnote of table 1, bpm: beats per minute, miss typing to bites per minute.

This has been corrected.

iii. 2nd paragraph. The authors described the comorbidity disorders of all patients, instead of list these diseases as patient demographics in 2 groups in table 1. Were these comorbidities evenly distributed in these 2 groups?

The information on this paragraph was intended to describe the sample of patients included in the study (elderly patients with comorbidities and polimedicated). The random assignation should have evenly distributed patients with these characteristics. However you are right that the description by treatment group may add information, and thus this has been added in table 1.

iv. Why not generate a table for the neurological complications, to make it easily to read and understand?

There were few complications reported and thus we consider that a narrative is easier to describe them.

All edits in the manuscript have been implemented as suggested.

Regarding the comment on the SPMSQ questionnaire: Pfeiffer et al described this questionnaire (ref 8) and defined the numbers of errors to consider normality (0-2 errors), mild impairment (3-4 errors), moderate impairment (5-7 errors) and severe impairment (8-10). The numbers of errors is adjusted according to level of educations (1 additional error is allowed in case of no elemental education and 1 error less is allowed in case of university education). The number of errors has
been indicated when referring to mild and moderate impairment in the text. Possible explanations to the fact that most patients improve their score are discussed in the discussion section.

A new table has been included to better explain the results of the SPMSQ, and the text has been modified.

Regarding your comment on the last paragraph, the text has been modified to explain that these are the results of a multivariate analysis to find out which variables predict the presence of intraoperative desaturation. Right hemisphere rCSO2 values at baseline were divided in quartiles, to estimate an OR with the highest quartile as reference value. This is why the numbers are given as fold increases in risk (interpretation of the OR) and it is not possible to mention the number of patients. Both the paragraph and table 4 have been slightly modified to make them more clear and readable.

6. Discussion

i. Usually in the first paragraph of discussion, we summarized the main findings and emphases the strengths of this study. Not necessary to re-iterate the study hypothesis and the aim to do this study. Please jump to your main findings and avoid unnecessary statements already shown in introduction section.

The first paragraph has been reviewed as suggested.

ii. One important issue worth of discussion is why patients receiving Bupivacaine had more neurological complications, in the condition that brain saturation is not different. Were your neurological evaluations adequate?

This finding has been commented in the discussion section. We hypothesize that these differences may be either related to lower SBP and MAP (although no statistically significant differences were observed between groups). We also comment that this may be an spurious finding, however we have not included any discussion on the validity of our measurements of neurological complications, which have only been recorded as reported by the physicians. Thus, we have added some discussion on this topic following your comments.

iii. Why in patients receiving GA, the cerebral oxygen reduction can predict the postoperative mentality decline, but not in this study.

In the study from Casati et al mentioned in the discussion, the desaturation observed, in terms of the number of patients presenting very low sRO2 values and the AUC were much higher than the ones observed in our study. Moreover, the study showed that monitorization of sRO2 values allowed to reduce the time the patient was desaturated thus preventing cognitive impairment in these patients. Few patients presented desaturation in our study and most were of mild intensity as patients were constatnly monitored and any desaturation was corrected. Thus, as patients are optimally monitored and treated, it is difficult to find differences between both treatments but also to find any relationship between desaturation and cognition in such controlled situation.
iv. You did not discuss the patients' characteristics difference in these 2 groups. More ASA 3 patients in B groups, this might be important confounding factors but being neglected. May be more comorbidities shown in B group patients. However, you did not compare and discuss this.

The CONSORT statement indicates that baseline information is most efficiently presented as descriptive statistics.

Actually, the tests of baseline characteristics are aimed at evaluating the quality of the allocation procedure, where the null hypothesis is that we expect no difference because of randomization, the alternative hypothesis is that the researcher applied inappropriate or fraudulent allocation procedures. Non-significant results cannot prove that patients were allocated randomly. It must also be considered that statistically significant baseline differences will occur even if the null hypothesis is true (randomization was correct).

In our study we have included descriptions of baseline variables per group (and added those related to comorbidities) however no statistical comparisons have been performed, as recommended by CONSORT.

To account for the possibility that any of the baseline variables might be confounding the results, an exploratory multivariate approach has been implemented

v. The authors stated that patient with Bupivacaine had lowest SBP than patient had LB, but lower BP was only short duration or persisted for a lengthy period was not mentioned. Perhaps an AUC is needed to show the significance, before jumping to the conclusion that the lowest BP was a key factor for neurological complications. (discussion, page 18, line 17-27)

Our data showed that the trough SBP measures were lower for B than for LB but no statistically significant differences were observed. The analysis of the trough values combined with the analysis of the AUC may have given a better measure of what is happening with BP under spinal anaesthesia and if there are differences between both local anesthetics. While this is a limitation of the study, this was not considered as one of the objectives and thus was not analyzed in this way. In the discussion we only point that this difference may have accounted for the differences in the incidence of neurological complications, but no other conclusion has been drawn from this results.

On the other hand, lower intraoperative MAP values were shown to be related with desaturation thus we suggest that the monitoring of MAP may be more relevant than the monitoring of SBP. However we are right that we are drawing some conclusions based on very weak evidences, and thus this reference to the need of monitoring the MAP has been eliminated.

vi. This study found an interesting finding of the association of the incidence of cerebral desaturation (rCSO2 score) and baseline right hemisphere rCSO2 score. However, the authors did not find any possible explanations for association. This part of discussion is under-developing.

We could not find any explanation for this finding, but we speculate that low levels of sCSO2 in the right hemisphere may be indicating the presence of an asymmetry between left and right
values (values lower in the right hemisphere than in the right hemisphere). This has been found related with memory impairment. However, this is very speculative.

7. Conclusion

i. I think the only conclusion the authors can make is that the regional cerebral saturation was not different in patient receiving B or LB for spinal anesthesia in elderly. Moreover, rCSO2 is not sensitive for predicting late neurological complications.

The conclusions have been rewritten following your comments.

8. The written language needs a thorough revision by a native speaking professional. Its credibility and readability would benefit from this.

The written language has been thoroughly reviewed and some edits have been made.

Wolfgang Buhre (Reviewer 2): In their interesting study the authors compared the effects of bupivacaine and levobupivacaine administered in geriatric patients undergoing spinal anaesthesia for hip fracture surgery. The study is of interest, as patients undergoing hip fracture surgery represent a 'frailty' population with a both a high risk of mortality as well as some risk to develop cognitive dysfunction after surgery.

This study has an interesting approach as the authors combined a haemodynamic study with measurements of cerebral perfusion and some testing for neurocognitive function.

In general, the manuscript is well written and the study methodology as well as the statistical analysis is well done. Moreover, it is interesting that two different local anaesthetics are compared which are both widely used in clinical practice. The authors has to be congratulated with the performance of this, quite complex study in a difficult scientific field in particular in patients undergoing emergency surgery.

Despite this there are some questions with respect to study protocol and conduct of the trial.

Thanks for your review. We hope that our answers and the new manuscript meet your expectations.

1. The authors used the SPMSQ, a. can you explain why patient with low scores were excluded (Methods section, first measurement was done before surgery, did the patient receive any pain therapy which can interact with the SPMSQ on beforehand. I think the problems of the SPMSQ in this setting as nicely given by the authors in the discussion chapter should be presented more pronounced.
As one of the objectives of the trial was to assess how cognitive function was affected after spinal surgery, those patients already with very deteriorated cognitive function (as assessed by SPMSQ with 8-10 errors) were excluded, as their cognition is already seriously deteriorated and thus there is no further possibility for change. As is has been mentioned in the discussion, the measurements before surgery may be influenced by different factors (such as pain and anxiety, intake of different analgesics and sedating drugs..) and may not represent the status of the patients before hospital admission. The text has been reviewed, emphasizing these aspects.

2. One important factor may be the time delay between trauma and surgery, can you describe this

The majority of patients were operated on within 2 days after admission. Also, the time from admission to surgery was distributed equally in both treatment groups, and no correlation between time to surgery and baseline SPMSQ scores were observed. This has been included in the results section.

3. The prehydration was 300 ml ringer’s lactate. Can the authors describe why they used this amount of fluids and moreover give some informations about the relation to body weight or mass

We provided tailored prehydration. In the elderly patient, preloading has been shown not always to be effective. Coe and Revanas (1) reported that in elderly ASA 1-3 patients, preloading with 16 ml/kg was no better than with 0 or 8 ml/kg. The practice of giving intravenous fluids prior to subarachnoid block only serves to cause large increases in central venous pressure of up to 15-20 cmH2O but blood pressure falls nevertheless because of a substantial decrease in systemic vascular resistance (2-3). Furthermore, if there is any delay in performing the intrathecal injection, which is quite probable when the patient is elderly and has age-related osteoarthritic changes to their lumbar spine, much of this fluid preload will redistribute to the extracellular fluid hence reducing the potential benefits of preloading.


4. Interestingly, there are some reports describing a relation between the use of phenylephrine and a decrease in NIRS-saturation (Immink et al., BJA) so please explain why PE instead of early ephedrine or even noradrenaline was preferred.
We used phenylephrine in our routine practice since the decrease of systemic vascular resistance is the main cause of hypotension in aged patient (1).

Various adrenergic agonists (ephedrine, metaraminol, methoxamine, phenylephrine, epinephrine) have been used either prophylactically or as treatment of hypotension of spinal anesthesia (HSA). Ephedrine, although probably the most commonly used pressor for HSA, may not in fact be the agent of choice in this situation. It is not a potent vasoconstrictor and thus does not well address the primary mechanism of the hypotension, which is the decrease in systemic vascular resistance (2,3). Careful study has indeed shown that ephedrine may not reliably reverse HSA (4,5).

The reference you make to the publication of Immink et al., BJA (Pennekamp C. W. A, Immink R. V, Moll F. L, Buhre W. F, de Borst G. J. BJA2012;109(5):831-3) reports a small case series (11 patients). In patients with intact cerebral autoregulation, the decrease in rSO2 after phenylephrine was associated with concordant changes in CO, whereas rSO2 remained unchanged when CO remained constant after treatment with ephedrine. The decrease in rSO2 after phenylephrine could be explained by a direct a-receptor-mediated cerebral vaso- constriction, as a decrease in middle cerebral artery diameter might result in a decreased blood flow, while Vmean remains constant or even increases. Based on these results, the authors conclude that the value of phenylephrine in terms of benefit for cerebral haemodynamics could be questioned.

However, phenylephrine is still a standard in our daily practice. The aim of our study was to compare two local anesthetics regarding rSO2 in elderly patients following our daily clinical practice and following the protocols in our centre. Hypotension is a frequent complication in this situation and in our study it was treated according to our protocols: phenylephrine and ephedrine was administered only in case the hypotension did not revert.


5. The authors describe that they use a fixed dose of midazolam and propofol in case of insufficient analgesia. Despite the fact that these drugs are not known for having analgesic properties, I wonder if the authors can discuss the additive value of sedation in this patient population.

Only 3 patients in LB group and 1 in B group needed MDZ and propofol. Both drugs are not analgesics but are useful to reduce anxiety that some patients present due to the sensitivity to touch at the start of surgery, and this is the reason why we refer to “insufficient analgesia”.

6. Is there any knowledge on the validity of the SPMSQ in this setting?

SPMSQ has been used as a standard to quantify cognitive impairment in different settings and in older surgical patients has been shown to predict clinical outcomes, thus it is considered a valid tool to be used clinically. However in our study we conclude that the “acute” situation of the patient at the baseline measurement and the “better” situation after the surgery (without complications in most cases) when the patient is transferred to a convalescence unit may have accounted for the unconclusive results obtained.