Author's response to reviews

Title: Transcranial Doppler to Assess Sepsis Associated Encephalopathy in Critically Ill Patients.

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Author's response to reviews: see over
Reviewer: Luzius Steiner

Reviewer's report:

The authors present data showing that a higher pulsatility index in the middle cerebral artery on day one after diagnosis of sepsis is associated with development of sepsis associated delirium. The presented data are interesting, yet to me the arguments that this is a robust relationship and not simply a reflection of more severe disease are not quite convincing:

Major compulsory revisions
1. I am somewhat surprised by the data in Table 1: A relevant number of patients is in septic shock, yet the CRP values and mortality suggest that the patients were not very ill. Please comment.

**Answer:** The CRP that is presented in Table 1 represents the maximum CRP value within the first 48h (we added this to the explications of the table). We found not statistical differences between the two groups. We think that an isolated value of CRP is not a good biomarker to evaluate the severity of septic patients; possibly the time course of CRP is more useful (Lelubre C. et al BMRI 2013). Nevertheless we presented the maximum value as an indication that both groups presented important signs of sepsis. Patients with PI> 1.3 presented a higher ICU and hospital mortality compared to other patients (36% vs 18% and 45% vs 18%, respectively). Our study did not have sufficient power to show a statistical difference in the mortality as this was out of the scope of this study.

2. Please add data on vasoactive drugs. How do you know that your changes in PI are not a reflection of more severe disease and use of vasoactive drugs?

**Answer:** We defined septic shock the need of support with vasoactive agents more than 0.1µg/kg/min. (We added this to the methods). We agree with the reviewer that increase PI may reflect the use of vasoactive drugs, even though results of a previous study (Pirrakos C et al AIC 2013) do not support this hypothesis. The aim of our study was to assess the correlation of PI with clinical signs of sepsis and not to investigate the causes of the cerebral microcirculation alterations in sepsis. We think that a differently designed study is needed to evaluate the effect of different factors (e.g. noradrenaline) on PI in septic patients.

3. Please add a sample size calculation. Is your sample sufficiently large to exclude a type II error in your multivariate analysis?

**Answer:** We added this calculation. Our sample is sufficiently large to exclude a type II error.

Minor essential revisions
4. Your Determination of PI is based on a very brief recording. Do you think this is representative? Please comment.
Answer: We tried to assess PI as an easily applicable and clinical relevant method to evaluate cerebrovascular constriction in septic patients. For longer recordings possibly a special frame is needed to fix the probe, something that is not easily applicable in not sedated patients. However we think that this limitation has only minor effect on the results of our study as we evaluated patients in stable hemodynamic and respiratory conditions. (We added this comment in limitations).

5. How many times per day did you perform the CAM ICU Screening?

Answer: We evaluated one time per day each patient but on the same time of the day. (Between 11:00-14:00) (We added this to the methods).

6. p.4/5 you write "Given that we evaluated static PI, we expected that an increased PI will be related to relative prolonged microcirculation disturbances and cerebral hypoxia. Therefore, we expected that neurological symptoms might be persistent or even present later than the initial measurement" As you are not measuring cerebral hypoxia, this sentence needs to be changed or moved to the introduction

Answer: We agree with the reviewer. We eliminated “…and cerebral hypoxia.”

Level of interest: An article of limited interest
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'