Author's response to reviews

Title: Continuous central venous oxygen saturation assisted intraoperative hemodynamic management during major abdominal surgery: a randomized, controlled trial

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Author's response to reviews: see over
Dear Editor and Reviewers,

Thank you for your comments regarding our manuscript „Continuous central venous oxygen saturation assisted intraoperative hemodynamic management during major abdominal surgery: a randomized, controlled trial”.

Please find our point-by-point responses below:

Editor’s comments:

Please acknowledge anyone who contributed towards the article by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include the source(s) of funding for each author, and for the manuscript preparation. Authors must describe the role of the funding body, if any, in design, in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. Please also acknowledge anyone who contributed materials essential for the study. If a language editor has made significant revision of the manuscript, we recommend that you acknowledge the editor by name, where possible.

There was no one else contributing towards the article apart from the authors mentioned in the „Author’s contribution” paragraph. No funding bodies were involved during the study and the manuscript preparation.

As suggested by Reviewer 1, language editing has been performed by Mrs Harriet Adamson.

The role of a scientific (medical) writer must be included in the acknowledgements section, including their source(s) of funding. We suggest wording such as ‘We thank Jane Doe who provided medical writing services on behalf of XYZ Pharmaceuticals Ltd.’

Non applicable, as no scientific (medical) writer has helped us prepare the manuscript.

An „Acknowledgements” section was added to the manuscript as follows:

“Acknowledgements

No funding bodies were involved during the preparation and conduction of our study. We would like to thank Mrs. Harriet Adamson in helping us as a language editor finalizing our manuscript.”

Responses to reviewers:

Reviewer #1:

1. Is the question posed by the authors well defined?

Yes, but inconsistence throughout the paper. The main objective of the study is to evaluate the use of intraoperative ScvO2 in reducing the first 2 days after the operations. This is what they
used to calculate the sample size on page 8 line 7. But it was not consistence with the aim in the abstract (page 2, line 4).

Thank you very much for noticing this inconsistency. Abstract was modified as follows:

“Our aim was to compare the effects of central venous pressure (CVP), and central venous oxygen saturation (ScvO₂)-assisted fluid therapy on postoperative complications in patients undergoing high risk surgery”.

2. Are the methods appropriate and well described?
Yes

3. Are the data sound?
Yes, but I still wonder how many patient never had hypotension throughout the operation.

Regarding the intraoperative hypotension the following data was added to the manuscript: Results (page10 line19)

“Although less patients had at least one hypotensive episode during surgery in the ScvO₂ group (17 vs. 25 in the control group), this difference was not statistically significant (p=0.18).”

4. Do the figures appear to be genuine, i.e. without evidence of manipulation?
Yes.

5. Does the manuscript adhere to the relevant standards for reporting and data deposition?
Only some parts. They need to add the consort figure, the randomization sequence generation, allocation concealment and funding source.

The following CONSORT flowchart was added to the manuscript, as Figure 2.

Regarding the randomization sequence generation and allocation concealment (page5 line21):
“Patients were randomly allocated by envelope randomisation in a block-of-ten fashion into control, or ScvO₂ groups.”

No funding source was used during the study, as indicated above and was included in the Acknowledgments section.

6. Are the discussion and conclusions well balanced and adequately supported by the data?
   Yes.

7. Are limitations of the work clearly stated?
   Yes.

8. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
   Yes.

9. Do the title and abstract accurately convey what has been found?
   Inconsistency corrected in abstract as above.

10. Is the writing acceptable?
    No, it needs major revision by native spoken.

We’ve kindly asked Mrs. Harriet Adamson who revised our manuscript as a language editor, as indicated in the Acknowledgements section.

Minor Essential Revisions

The abstract should be rewritten;

1. The aim is not well described (page 2 line 4)
   Inconsistency corrected in abstract as above.

2. The main outcome should be presented at the beginning of the results.
3. The conclusion should be changed because there was a statistically significant in postoperative PaO₂/FiO₂ ratio and survival (table 1). Though the other complication was not (table 3).

Thank you very much for these comments. The Results and Conclusion parts of the abstract were modified as follows:

**Results:** We observed a lower number of patients with complications in the ScvO₂ group compared to the control group, however it did not reach statistical significance (ScvO₂ group: 10 vs. control group: 19; p=0.07). Patients in the ScvO₂ group (n=38) received more colloids compared to the control group (n=41) [279(161) vs. 107(250) ml/hour; p<0.001]. Both groups received similar amounts of
crystalloid (1126±471 vs. 1049±431 ml/hour; p=0.46) and norepinephrine [37(107) vs. 18(73) mcg/hour; p=0.84]. Despite similar blood loss in both groups, the ScvO₂ group received more blood transfusions (ScvO₂ group: 63% vs. control group: 37%; p=0.018). More patients in the control group had a postoperative PaO₂/FiO₂<200mmHg (23 vs. 10, p<0.01). Twenty eight day survival was significantly higher in the ScvO₂ group (37/38 vs. 33/41 p=0.018)

**Conclusion:** ScvO₂-assisted intraoperative haemodynamic support provided some benefits, including significantly better postoperative oxygenation and 28 day survival rate, compared to CVP-assisted therapy without a significant effect on postoperative complications during major abdominal surgery.

The table

*should be put after p-value that were < 0.05

Significant differences now marked with * in figures and tables.

**What is the definition of severe hypotension in page 7, line 13?**

Thank you for this question, we did not describe this topic precisely enough. In cases of hypotension requiring fluid administration either indicated by low ScvO₂ in the ScvO₂ group or low CVP in the control group, the protocol allowed the anaesthetist to use vasopressors if the hypotension did not seem to improve quickly enough by the fluid administration alone. It was the clinical judgement of the anaesthetist responsible for the patient. The definition was MAP < 60 mmHg, similarly to the definition of the protocol. We tried to clarify it in the manuscript as follows:

(Page8 line1)

“It is important to note that in cases of persistent hypotension treated by the fluid bolus as per the study protocol, anaesthetists were allowed to administer norepinephrine boluses in both groups and the amount given was recorded and added to the total dose calculated at the end of surgery.”

**Please give more details about postoperative course.**

- Does every patient extubated and what about the oxygen supplementation? Does there any different between the 2 groups?

- Does every patient go to the ICU?

All patients were admitted to the ICU following the operation as described in the Patients section Page5 line10 (‘all’ word added).

Regarding the extubation and oxygen supplementation the following information was added (Page10 Line1):
“Five patients in the control group were not extubated at the end of the surgery, 4 of whom were extubated on the first postoperative day and one patient was ventilated for 11 days. In the ScvO₂ group, all patients were extubated at the end of surgery apart from 2 patients who were extubated on the first postoperative day and 1 patient who was ventilated for 3 days. Following extubation all patients received oxygen supplementation via a 28% or 40% Venturi face mask to maintain SaO₂ > 94%.”

We would like to also thank you for the highlighted mistypes and errors in our manuscript which were corrected.

Reviewer #2:

1- Authors should rewrite their hypothesis because intensive care datas are not include their hypothesis.

The Reviewer is right, and we also agree. This is why we emphasised it in the Introduction that: “Advanced hemodynamic monitoring, using cardiac output, stroke volume, stroke volume variation (SVV), pulse pressure variation (PPV) to guide intraoperative fluid therapy resulted in improved outcomes in several studies [11,12,13,14].” and also that: “It is well known, that using heart rate (HR), mean arterial pressure (MAP) and central venous pressure (CVP) only to assess and guide haemodynamic support may be misleading [8,9,10].” However, the Reviewer is right, that the explanation of our hypothesis/aim is lacking a bit more support. Therefore, we changed the sentence before our hypothesis as such (page 4, line 19):

“Despite these theoretical advantages, ScvO₂ is only used in 12-30% of high risk surgical patients [15]. In clinical routine, MAP and CVP are the most frequently applied monitoring tools (75-95%) during high risk surgery [15], despite convincing evidence that neither can predict fluid responsiveness [8, 9, 10].

Therefore, the aim of the current study was to compare the effects of ScvO₂ assisted intraoperative haemodynamic support to the routinely used MAP-CVP approach on postoperative complications in high risk surgical patients.”
We hope this addition the aim of the study clearer.

2- Did authours registered to clinical trials?

Yes, the registration information are now included into the abstract (ClinicalTrials.gov Identifier: NCT02337010)

3- Is this trial retrospective or prospective.? Authours should add in material methods section.

This is a prospective study, information added to Methods section (Page5 Line10)

4- How will authours explain, control groups had higher hb levels than ScvO2 group? And They used more blood in ScVO2 group? Because 2 groups lossed the same amounts blood during the operation. I think hemodilution is insufficient for explain.

6- Authours should add time of blood and blood product in their flow chart.

7- Did control group have dehydratation? Because at the end of the surgery both groups had the same Hb levels.

Thank you for raising these issues. We would like to answer these questions together because they basically cover similar topics.

Haemoglobin levels showed no significant difference at the start and at the end of the operation. The indication for blood transfusion is not included in the flowchart of the study protocol as in both groups it was a haemoglobin level lower than 80 g/l regardless of the haemodynamic parameters. And finally, we didn’t observe obvious dehydration in any of the patients.

As there was no difference in the initial haemoglobin levels and the intraoperative blood loss, we were not able to identify any other explanation as to why more patients reached the 80 g/l threshold in the ScvO₂ group compared to the control group, other than the dilutional effect of the colloids given. In a study conducted in patients undergoing radical cystectomy, using the same colloid solution replacing the blood loss in a 1:1 ratio, following the administration of 1600 ml of colloid the authors observed a dilutional effect of 30% based on the measured haematocrit levels. (Fenger-Eriksen C et al Journal of Thrombosis and Haemostasis 2009(7):795–802). In our study, patients in the ScvO₂ group received approximately 500 ml more colloid solution on average during surgery compared to the control group. Our explanation for this “more fluid, more blood” situation is, that on the one hand hypovolemia caused a drop in the ScvO₂ due to impaired oxygen delivery, which remained unidentified in the CVP group. On the other hand, this extra fluid may had a dilutional effect, which could have led to the more frequent decrease of haemoglobin levels <80 g/l in the ScvO₂ group.

The above hypothesis is briefly summarised in the Discussion (page13, line8):

“As there was no difference between the groups in the haemoglobin levels at the start and at the end of the operation, and the intraoperative blood loss was similar in both groups, the increased use of fluid in the ScvO₂ group may had caused dilutional anaemia and the need for more frequent transfusion in this group.”

5- Why did they use more fentanly in ScVO2 group?
There was no significant difference in the dose of fentanyl given, as indicated on Page11 Line12:

“There was no difference regarding the dose of fentanyl used during the operation (ScvO\textsubscript{2}: 179 \pm 70 mcg/h vs. control: 167 \pm 77 mcg/h, p=0.06).”

8- Did authors measure ScVO\textsubscript{2} in control group? This subject is not clear. In group ScVO\textsubscript{2} MAP level was higher than control group. And in control group CVP level was lower than ScVO\textsubscript{2} group. How authors will explain this status?

The continuous measurement of ScvO\textsubscript{2} was used in the ScvO\textsubscript{2} group only. In the control group the level of ScvO\textsubscript{2} was not part of the haemodynamic management. However, we measured its level hourly in the control group too and compared the levels measured during the operation on Figure 3.

Page 6 Line 20:

“Central venous saturation was continuously monitored in the ScvO\textsubscript{2} group by using a CeVOX monitor (Pulsion Medical Systems, Munich, Germany). The CeVOX probe (PV2022-37; Pulsion Medical Systems, Munich, Germany) was inserted into the internal jugular central venous catheter as described in the manufacturer’s users manual. The position of the central venous catheter in the superior vena cava was confirmed by chest X-ray postoperatively. The system was calibrated in vivo for ScvO\textsubscript{2} measurements by laboratory co-oximeter (Cobas b 221, Roche Ltd, Basel, Switzerland). Calibration, if necessary, was repeated at least hourly during the surgical procedure. In the control group the level of central venous saturation was measured hourly by laboratory co-oximeter.”

There was no significant difference in the level of MAP and CVP as seen on Figures 4 and 5 in the revised manuscript.

9- Operations time were very long than normal operations time. Operation time is related morbidity and mortality in major surgery.

We agree with the Reviewer. This was one of the reasons why we became interested in this topic. As operation time is basically independent from anaesthesia, our idea was whether optimising intraoperative haemodynamics could reduce perioperative morbidity, hence mortality.

To note, the average operation time in our study (~250 min) was shorter than in the study by Fenger-Eriksen C et al., on haemodilution in total cystectomy cited above, which was 312 minutes. However, we don’t feel it should be discussed in the text as the study population in the two trials were different.

10- Did their oesophagectomy operations had thoracotomy?

Only one of the 6 patients who underwent oesophagectomy had a thoracotomy with one lung ventilation. He was randomised to the control group.

11- Authors should excluded radical systectomy.
The Reviewer is right that including patients undergoing several types of surgery in general may dilute the data, makes the population heterogeneous, and hence may increase the noise-signal ratio. However, including patients undergoing only one type of surgical intervention would inevitably have limited the general message of the study and reduced recruitment rate. As our university is a centre for radical cystectomy, we felt that a very important subgroup would have been lost if we had excluded them.

Furthermore, the Reviewer is also right, that intraoperative urine output is difficult, or cannot be measured in these patients. Urine output wasn’t an end-point of the study, however from many other aspects (duration of surgery, the magnitude of surgical insult, fluid loss, etc) these patients were “ideal” subjects for answering our questions (apart from analysing the intraoperative urine production).

Finally we would like to thank the Editor and the Reviewers for taking the time and effort in helping us with these important comments, which we hope improved the manuscript substantially.