Author's response to reviews

Title: Ringer's lactate but not hydroxyethyl starch prolongs the food intolerance time after major abdominal surgery

Authors:

Yuhong Li (yuh_li@qq.com)
Rui He (15347172@qq.com)
Xiaojian Ying (1250700404@qq.com)
Robert G. Hahn (r.hahn@telia.com)

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Author's response to reviews: see over
Author responses to reviewer criticism concerning the manuscript entitled “Ringer’s lactate but not hydroxyethyl starch prolongs the food intolerance time after major abdominal surgery”

Reviewer 1

**Reviewer's report**
**Title:** Ringer's lactate but not hydroxyethyl starch prolongs the food intolerance time after major abdominal surgery
**Version:** 2
**Date:** 15 October 2014
**Reviewer:** Nayer Youssef

**Reviewer's report:**
Dear Author,
It was a great pleasure and honor reviewing this paper. On the overall, good work. Find below my notes regarding your manuscript.

Major Compulsory revisions:
1- Page 3 line 19-26: This paragraph is a redundant repetition of the methodology. The introduction should be more about presenting a background of the topic and highlight the conflict and how this study will help resolve that conflict.

**Answer:** These lines have been removed and the *Introduction* markedly expanded with respect to background. In fact, it is quite common to include a couple of lines explained the set-up of the study if being on the complex side, but we agree that this amount of text was too long.

2- I think the question need to be more framed in the text especially that the FDA had a black box warning published in Nov. 2013 re: increased mortality, renal injury and risk of bleeding for the use of HES in some settings

**Answer:** In a way we count on that the readers are aware of these warnings. However, we have added some passages with reference to the recommendations and
cite the recommendations given by the European Medicines Agency in the very first section of the Introduction.

3- Page 4 line 5: the author needs to comment on the sample size (either here or in the discussion How did you reach that number? is it too small or adequate? Did it affect the results?
Answer: The study was originally powered to disclose differences in haemodynamic response between those who received Ringer’s lactate and hydroxyethyl starch during the bolus infusions (see parent publication). We have now inserted a post hoc power analysis to show by which certainty the main outcome measure was reached.

4- Page 5 line 1: The author needs to mention some information regarding postoperative analgesia and weather any long acting opioids or PCA were used that would affect bowel function.
Answer: Information about postoperative analgesia is now given by the following specification:

“Postoperative pain relief was managed by patient controlled intravenous analgesia (PCA) using sufentanil 100 µg in 100 ml in isotonic saline which was given at a rate of 2 ml/h. Bolus injections were 2 ml using a lockout-time of 5 min and a maximum of 30 ml during 4 hours,”

5- Page 4 line 7: The discussion should include an explanation for choosing to conduct an open-labelled trial and the challenges of doing this as an RCT, sources of Bias and how this would affect the results

Answer: These issues are now discussed in the Limitations section. The main reason for the set-up is that the study was originally planned to disclose haemodynamic differences in the beginning of these operations, when the patients were under general anaesthesia and the data recorded digitally. Inference on part of the investigators in such a strictly controlled setting is quite unlikely and hardly makes up for the problems involved in using blinded bags.

Minor Essential revisions:
1- Page 4 line 8: You can’t call it IV general anesthesia if you used 1-2% of Sevoflurane for maintenance
Answer: We now state that the patients had a combined intravenous and inhalational general anaesthesia.

2- Page 4 line 9-10: The author needs to clarify defining obstructive pulmonary disease by airway pressure> 25. Is it the baseline after intubation or preop. And I would suggest adding a reference for that number.
Answer: The specification of this pressure has been deleted as we could not find an appropriate reference. In any event, exclusion because of obstructive lung disease is not normally made by measuring the airway pressure – this diagnosis is based on other measures such as anamnesis, lung auskultation, and $\text{FEV}_{1.0}$.

3- Page 5 line 25-28: please clarify the value of preloading group 2 with RL (can be done in the discussion)

Answer: This is now explained in the Limitations section by the following phrase: “We also had an interest in evaluating the importance of dehydration on the results, which was done by providing a slow drip of 500 ml of Ringer’s lactate a few hours before the surgery.” This interest was simulated by Reference 15 in which preoperative dehydration greatly increased the number of complications after hip fracture surgery.

4- Page 6 line 18: I think that both the need for pain relief which can be affecting bowel function and blood transfusions which can be a reflection of coagulopathy caused by HES should be counted for.

Answer: A large haemorrhage volume can be a complication, while the need for transfusion is dependent on the preoperative Hb concentration and the target Hb chosen in the individual patients.

Table 1 gives the number of postoperative bleeding complications and the amount of transfused erythrocytes and plasma. These were evenly distributed among the groups. The amount of blood loss during the surgery was very small (average 200 ml), which is also given in Table 1.

Discretionary revisions:
1- Page 4 line 22: I think “Patients were NPO overnight or for X-hours” sounds like a more simple structure

Answer: I don’t understand this notion. NPO (Nil per os)?
Reviewer's report

Title: Ringer's lactate but not hydroxyethyl starch prolongs the food intolerance time after major abdominal surgery

Version: 2 Date: 29 December 2014

Reviewer: Michael James

Reviewer's report:
This study evaluates the effects of varying combinations of crystalloids colloids on gut recovery following, predominantly, laparoscopic cancer surgery.

Minor essential revisions:

1. On page 4, lines 5-19, the authors state that 111 patients were initially recruited but only 88 actually studied for technical reasons. Were these 111 patients randomised or were only the subsequent 88 patients randomised. If all 111 were included, what happened to the randomisation sequence and how was this adjusted to account for the subsequent exclusion of these patients. This would also preclude an intention-to-treat analysis and these issues should be clarified. If only 88 patients were actually randomised, then reference to the 111 patients is merely confusing and does not add to the scientific value of the paper.

Answer: The notion of the 111 patient has been removed and now only 88 are mentioned, except in the Limitations section where it is explained that first 23 patients had to be excluded in that the main author changed hospital and that data on the postoperative course (including complications, blood transfusions etc.) could no longer be obtained from the first hospital.

The issue with the randomisation is now explained in the Methods section. Patients were confined in blocks of 25-30 to the four treatment groups, but the second-line infusion (continuous infusion) was randomized. We apologise for not being clear on this issue.

2. The statistical section is not satisfactory. How did the authors arrive at the number of patients studied? Was a power calculation performed and if so what parameters were used? Categorical comparisons such as the number of complications are presented, but these would require additional statistical methods to those described. This section needs to be rewritten and expanded.

Answer: The power analysis in now explained in the Statistics section. We have also illustrated some data with ROC to support what is, in fact, also said by the ANOVA analyses. The only categorical comparison is between complications/no complications (group variable) and the relation to fluid volumes (predictor). This is readily performed by ANOVA.
3. Haemodynamic monitoring was conducted using the Vigileo system, but no results are reported. Why is this? The authors should either present these data or justify their omission.

Answer: The reason for the Vigileo was to monitor the haemodynamics during the first part of the study, which result is presented as Reference 16. This is now explained, and details about the apparatuses tuned down in the Methods section as haemodynamic data are not reported here.

4. The problem of the terms restrictive and liberal is addressed on page 10 lines 19-25. For example, although the study by Varadhan & Lobo showed that up to 2.75 L per day were associated with better outcomes, this was referred to as restricted fluid therapy, whereas the study by Holte et al was described as using liberal fluid therapy but almost identical volumes (2.5-3 L per day) were used. It would be better to avoid liberal and restrictive and rather refer to actual volumes. The authors might like to consider referring to the more recent concept of zero balance which has been nicely summarised in a recent publication. {Miller, 2014 #4528}

Answer: The word “liberal” is now removed albeit “restrictive” is mentioned in a few places. The new paper about zero balance is now cited, together with the paper in which we first saw this expression.

5. On page 11, lines 9-22, the authors address the issue of better urine output in the starch group. One possible explanation that has not been considered is the fact that haemodynamics may have been better in the starch group, particularly renal perfusion. This should at least be addressed in the discussion.

Answer: This is a good suggestion. The renal perfusion is now mentioned.

6. The authors state that crystalloid blood replacement requires 3:1 proportion of fluid, whereas colloid replacement requires only 1:1. Whilst this is in line with general physiology, it has been challenged as a principle and the authors should give a reference to support this and I would suggest a recent paper by Roger et al is appropriate. {Roger, 2014 #3719}

Answer: We cannot locate this publication. The last author in the present work has published papers indicating that 2:1 would be more appropriate than 3:1 (Acta Anaesthesiol Scand 2013; 57: 16-28 and Anaesthesiol Intensive Ther 2014; 46: 342-349) but we feel that such a discussion is out of the scope of this presentation.
7. The details of the fluid therapy are somewhat difficult to follow and it would be substantially clearer if the groups were defined at the beginning of this paragraph. In other words, it would read better if lines 1-6 from page 6 were moved up to the beginning of the Fluid Therapy paragraph.  

Answer: Done.

8. On page 7, lines 23-26 the authors state that 66 patients who received # 1 L starch had shorter PACU times. It appears from the protocol that no patient received less than 1 L starch, so this could be simply stated as 66 patients who received starch. If my interpretation is incorrect this should be clarified.

Answer: This is a misunderstanding. When reviewing the original data set, it appears that 3 patients received no starch, 19 patients received 500 ml, 58 received 1000 ml, and 8 received 1500 ml. Those who received no starch were in Group 4.
Reviewer 3

Reviewer's report
Title: Ringer's lactate but not hydroxyethyl starch prolongs the food intolerance time after major abdominal surgery
Version: 2 Date: 11 January 2015
Reviewer: Massimiliano Greco
Reviewer's report:
Major Compulsory Revisions
For the moment I raise the following questions
1) The final paragraph of the introduction, after the research question "The present study explores whether starting the fluid therapy with starch or 18 Ringer’s lactate has an impact on postoperative GI recovery and surgical complications.” belong to the method section. Please remove it from the introduction.
Answer: Done.

2) The research question reported in the second sentence of the introduction paragraph of the abstract differs from what is specified in the article introduction and methods, leading the reader to ask himself which of the two was the research question
Answer: This is now rectified. The present report explores whether starting the fluid therapy with starch or Ringer’s lactate has an impact on postoperative GI recovery and surgical complications in a cohort of patients undergoing major abdominal surgery primarily by the laparoscopy.

3) The study is defined as “open-labelled clinical trial” in the introduction, while in the methods is specified that “The anaesthesia and research were managed by anaesthetists blinded to the preloading”. I cannot understand if this study was open or blinded, and then who was blinded to the research. Please specify (note that on the Chinese Clinical Trial registry this is also not specified.
Answer: Researchers were blinded was only to the preoperative preloading which was carried out a few hours before the surgery, but not to which fluid was used during the actual surgery. To avoid this confusion we remove the notion of blinding of the preloading part.

4) Was the study randomised? if yes, please specify how randomisation was performed, who generated the random number sequence, and how allocation concealment was granted. Moreover, please specify why in the Registry you have stated that this study was not randomized. If it is not randomised, please remove any reference to randomisation concerning this article, and specify how patient were allocated to the different groups.
**Answer:** We apologise for the confusion here, and the presence and absence of randomisation is now better explained. Patients were randomised in blocks of 25–30 for the different treatments by the author YL. This means that patients were not randomized on an individual level but on a group level. On the other hand, the fluid given after the first volume optimization round and during the first hour of surgery was randomized in the individual level (in Groups 1 and 3).

**Minor concerns**

Figure 1 is repeated 2 times in my pdf, please check that only a figure 1 is included.

**Answer:** Done.