Author’s response to reviews

Title: The effect of low central venous pressure on hepatic surgical field bleeding and serum lactate in patients undergoing partial hepatectomy: a prospective randomized controlled trial

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Author’s response to reviews:

Dear Guangde Tu, PhD:

We are very grateful for reviewer’s comments about our manuscript No. BSUR-D-19-00459R1 Title: The effect of low central venous pressure on hepatic surgical field bleeding and serum lactate in patients undergoing partial hepatectomy: a prospective randomized controlled trial. According to reviewers’ advice, we amended the relevant part of the manuscript. The correction sections have been marked using red text in our revised manuscript. I have addressed each concern by reviewers’ and made responses to their comments individually as follows. Furthermore, we have capitalized the first letter of legend keys in figure 2 & 3.

ANSWER TO REVIEWER 1

Moritz Schmelzle (Reviewer 1): Thank you very much for you research and manuscript. The hypothesis, relevance, methods and outcomes are well described in a transparent and sufficient manner. Some revisions/additional aspects are listed below.

1. No postoperative follow-up is described. Lowering the intraoperative blood pressure might favor postoperative complications such as delirium or renal insufficiency. While possible positive effects of low central venous pressure and therefore also reduction of the organ perfusion pressure (best described as Mean art. Pressure) are clearly investigated, possible adverse effects are not.

Response: Thanks for the insightful comments and suggestions. These comments are all valuable for revising and improving our paper.
We agree with your comments. There is no way to reduce the central venous pressure (CVP) without affecting the patient's arterial blood pressure and patient's organ perfusion pressure. We took consider the adverse effect of lower CVP on the organ perfusion pressure when we designed this study. So, Ephedrine 6 mg was administered if systolic blood pressure (SBP) was less than 90 mmHg. When the urine output was less than 20 ml/h, an additional fluid infusion of 200 mL crystalline solution was quickly infused. Following the reviewer’s remark, the additional information about mean arterial pressure has been added into line 18-19 of page 7, line 3 of page 9, table 4, and section of List of abbreviations.

In order to collect the post-operative data, we followed the database of our hospital. The follow-up results were recorded and the outcome was evaluated. Lists are as follows: length of hospital stay after operation, pre-operative albumin, pre-operative total bilirubin, pre-operative alanine aminotransferase (ALT), pre-operative creatinine, pre-operative prothrombin time, post-operative total bilirubin, post-operative ALT, post-operative creatinine, post-operative prothrombin time. However, the time for the Laboratory tests after operation varied. We recorded post-operative results on the 7th day after operation. If the data on the 7th day after operation was not available, prior records were to be checked. We selected the data of the 6th day, 5th day, 4th day and 3rd day after operation in turn. And we recorded the post-operative days for Laboratory tests as well. The Mann–Whitney U test for two samples or the independent sample t-test were performed. The results show that there are no different between groups. We have listed a table about the post-operative data. However, I found that the table cannot be uploaded following the letter when I tried to paste a table. I can email the table if there is a need. (Uploaded by Editorial office, please find in supplementary files, at the end of this PDF file.)

We didn't think about the problem of postoperative follow-up when we designed the trial. Now no satisfactory postoperative data was obtained because the day of laboratory tests for postoperative patients is inconsistent. But we can get all the accurate data of postoperative patients at the post-anesthesia care unit. We have added the information (postoperative delirium, delayed recovery, urine output less than 20ml/h, and emergence agitation) at the post-anesthesia care unit on line 5-6, page 7 in the Method section; on line 6-7, page 10 in the Results section.

2. Under what circumstances was portal trail clamping applied? Was there a standardized protocol, e.g. matched to a score of the bleeding score of hepatic surgical field? Your data show that the PTC time was not lower in the group L (with fluid restriction AND lowered central venous pressure) which might indirectly show that surgical site bleeding was not reduced.

Response: We appreciate your comments. In the present study, the use of PTC (portal trail clamping) was determined according to the location and size of the liver mass by surgery. Thus, the choice of surgical procedures and PTC was not based on the purpose of the present study. Considering the reviewer’s suggestion, a new section addressing the portal trail clamping had implied in line 12-14, page 7.

It was the fact that the bleeding score of surgical fielding were significantly different between two groups (X2= 17.133, P=0.002). We have added the statistic method about the bleeding score
of surgical field in line 7, page 9 of Statistical analysis section, and in line 5-6 of page 10 of Results section.

A clean and dry surgical field should shorten the duration of PTC, however, there is no difference between the two groups. Our explanation is as follows. There was no patients’ surgical field bleeding score is 5 (severe bleeding, frequency aspiration required, very hard to perform surgery) in both groups. The number of patients with no bleeding and minor bleeding of surgical field (bleeding score≤3) is 55 (n=69) in group F, and 64 (n=70) in group L (see table 1 in revised manuscript). The minor bleeding of the incised liver surface may has little effect on the speed of the operation. This is our explanation for the same duration of PTC in two groups. If you have any question, please do not hesitate to contact us.

3. For representing non-normally distributed data we recommend using the median rather the mean value.

Response: Thanks for your suggestion. We are very sorry for our mistakes. Two data (duration of all PTC and CVP during PTC ) all were non-normally distributed data. We have amended the data information about “duration of all PTC” and “CVP during PTC” in table 4 by red marked. Further minor changes had been made on Line 5, page 9 in the Statistical analysis section and Line 21-22, page 12 in the Discussion section. These do not affect our interpretation of the result.

4. Resection extent and surgical approaches differ between groups and differences found might be biased, please comment in the Discussion section.

Response: Thanks for your advice. Mann-Whitney U test for two samples was performed to compare the extent of liver resections and the type of liver resection between groups. There were no difference in the extent of liver resections and the types of liver resection between two groups. The statistical method and result related to said data were not stated in the original manuscript. The statistical method has been added in line 4-5 of page 9. The statistical result has been added in line 16-18, page 9. The authors are grateful to the referees for pointing out our error.

4. Some grammatical errors are left to be corrected.

Response: We are very sorry for our incorrect writing. The grammatical errors had been revised in revised manuscript by Liwen Bianji, Edanz Editing China (www.liwenbianji.cn/ac). Once again, thank you very much for your comments and suggestions. We have studied your comments carefully and have made correction with red marked text which we hope meet with your approval.
Parissa Tabrizian (Reviewer 2): Tan et al designed a prospective randomized controlled study and evaluate the effect of fluid restriction alone versus fluid restriction + low central venous pressure on surgical field bleeding, intraoperative blood loss and serum lactate.

1. The study is overall well written and the topic remains controversial. The majority of the patients in this study had a minor hepatectomy and are non-cirrhotic. I am uncertain if a meaningful conclusion can be drawn based on these factors. is there a role in measuring CVPs in patients undergoing minor resections?

Response: Thanks for having reviewed our manuscript. These comments are very helpful for improving our paper and guiding to our researchers.

In our hospital, around 20% of our patients undergoing minor hepatectomy resection were without PTC (portal trail clamping). It is not necessary to control the value of CVP in such patients with minor hepatectomy without PTC. Patients with minor hepatectomy without portal trail clamping were not enrolled in this study. Patients undergoing elective partial hepatectomy with intraoperative PTC were enrolled in this study. In the present study, the use of portal trail clamping was determined according to the location and size of the liver mass by surgery. Thus, the choice of surgical procedures and PTC was not based on the purpose of this study. To clarify the criteria for enrolled patients, a new section addressing the portal trail clamping had described in line 12-14, page 7.

Indeed, measuring CVP is more meaningful for patients undergoing major section. However, surgical complexity is also related to the location of the liver malignancies. For example, central hepatic malignancies (in segment IV, V, VIII) is close to major vascular and biliary structures. Right-sided hepatectomy (in segment VI, VII) is related to deep location. The risk of blood loss may be higher in patients with central hepatic malignancies undergoing minor section( Lee SY., Central hepatectomy for centrally located malignant liver tumors: A systematic review. World J Hepatol. 2014 May 27; 6(5): 347–357). In this present study, there were two patients with 1200 blood loss, one patient underwent major resection (Extended left hepatectomy), whose operation time was 290 mins and duration of PTC is 35 mins, another patient underwent minor resection (partly central hepatectomy), whose operation time was 285 mins and duration of PTC is 59 mins. The longest operation time in patients with minor section is 330 mins, which equal to the longest operation time in patients with major section.

To reduce bleeding during liver resection, hepatic portal triad clamping is routinely used in half of medical centers (Mise Y, et al. A worldwide survey of the current daily practice in liver surgery. Liver Cancer. 2013; 2:55-66.). Minimizing blood loss should be a consideration of both the surgeon and anesthesiologist. When portal trial clamping was chosen by the surgeons to reduce the blood loss, it is necessary for anthologists to control the CVP.

2. Table 1/figure 1 can be deleted. It does not demonstrate an objective measure of blood loss

Response: Thank you for your question. We read the submission guide of “BMC surgery” carefully and found that the figure 1 (participant flow) is required for randomized controlled trials. So we kept this figure 1.
We agree with you that the data in table 1 cannot demonstrate an objective measure of blood loss. However, there is no accurate method for measuring intraoperative bleeding, especially the blood loss during a special surgical stage (the duration for liver mass resection). Furthermore, surgical field bleeding of the incised liver surface has related to the surgical field visibility. The fewer score of the surgical field, the drier and cleaner the surgical field was. After careful consideration, we prefer to retain the use of table 1. However, in order to describe clearly, we have added the statistical result in revised table 1.

According to your suggestion, we amended the paragraph about limitation of this study, see line 19-22, page 13 and line 1-3, page 14. If you still want us to remove or alter the table 1, please let us know. Thanks for your feedback.

3. The discussion segment is too long and need to be shortened

Response: We appreciate your comments. We have shortened the discussion segment as follows:

The 1st paragraph and the 2nd paragraph in the original manuscript: We have shortened and merged them into one paragraph in the Discussion section of revised manuscript.

The 2nd and 3th paragraph in the revised manuscript: We shortened both of them. We have amended some sentence in line 9-15, page 12 of 2nd paragraph.

The 5th paragraph in the revised manuscript: we have deleted some sentences and have added some information in line 15-18, page 13. The added reference (number of 25,26) have been amended in the Reference section.

The paragraph about the trial limitations: we amended this paragraph, see line 19-22, page 13 and line 1-3, page 14. We have deleted a whole paragraph (the 8th paragraph in original manuscript). We have deleted some sentences from the last paragraph in the revised manuscript in Discussion section.

The references from 24-28 were updated in the Reference section. We also updated the number of the reference in Reference section.

4 Few grammatical mistakes need to be corrected

Response: We are very sorry for our incorrect writing. In order to appreciate your valuable comments. The grammatical errors had been revised in revised manuscript by Liwen Bianji, Edanz Editing China (www.liwenbianji.cn/ac). Once again, thank you very much for your comments and suggestion.

5 Did you exclude repeat resections in your study?

Response: Thank you for your question. Patients with repeat hepatectomy, conjoined surgery were excluded in our study. We have added those in the Method section in revised manuscript. See page 5, line7-9.
6. It would be interesting to assess the long term outcomes in each group.

Response: We agree with your comments that the long-term outcomes are important for a patient with cancer. We are trying to follow the patients of this study for their long-term outcomes. However, we are sorry that we cannot offer the data about the long-term outcomes now. Post-operative time is too short to follow up the long-term outcomes, because of the patients enrolled in this study from December 2017 to April 2019. Furthermore, the type (primary hepatocellular carcinoma and colorectal cancer liver metastasis) and the stage of the liver cancer were not considered by us in this study. We prefer to cooperate with surgeons to assess the long-term outcomes in the future. If you are interested in the long-term outcomes, please connect with us by email: maggian@yeah.net.

We have studied your comments carefully and have made correction which we hope meet with your approval.