Author’s response to reviews

Title: Effect of restrictive fluid therapy with hydroxyethyl starch during esophagectomy on postoperative outcomes: a retrospective cohort study

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BSUR-D-18-00291, entitled “Effect of restrictive fluid therapy with hydroxyethyl starch during esophagectomy on postoperative outcomes: a retrospective cohort study”

Dear, Hayley Henderson

Editor of BMC Surgery

We would like to thank the Editor and Reviewers for their thoughtful review and appreciate the time and effort they dedicated on our manuscript. We revised and are re-submitting the manuscript based on these advices and suggestions to be considered for publication in BMC Surgery.

Please see below, our responses to these remarks. We attempted to comprehensively address each point and made appropriate changes to the text. We thank you for considering our manuscript for publication in BMC Surgery.
Yours sincerely,

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To Reviewer #1:

Noriyuki Hirahara, Ph.D., M.D. (Reviewer 1): Well written

Response: We greatly appreciate your thoughtful comments.

To Reviewer #2:

Toshiya Kamiyama, Ph.D (Reviewer 2): The authors described about effect of restrictive fluid therapy with hydroxyethyl starch during esophagectomy on postoperative outcome. Intravenous hydroxyethyl starch infusion is associated with an increasing risk of postoperative composite complication. This article is well-written and interesting.

Response: We greatly appreciate your thoughtful comments.

Major limitation

1. This study may be collaborative research on many facilities. So, how does the authors guarantee the quality of operation and postoperative management.

Response: Thank you for the comment. This study is a study conducted at a single institution and esophageal surgery and perioperative management were performed by a single team including experienced surgeons, anesthesiologists, and intensivists. Therefore, we think that it is unlikely that our results may be attributed to differences in the quality of operation and postoperative management. However, to clarify, we revised the Methods section as follows.
After approved by the Institutional Review Board of our institution (AMC IRB 2016-1324), we performed a single-center retrospective observational study including all patients aged ≥ 20 years who underwent elective esophageal surgery at our institution between January 2005 and October 2015.

Esophageal surgery and perioperative management were performed in the standard manner as previously described in details [10]. Briefly, all operations were performed by experienced surgeons and anesthesia was maintained by either volatile anesthetic agent or intravenous anesthetic agent. In all patients, opioid (remifentanil) was administered continuously during surgery and the dosage range was adjusted by assessing hemodynamic parameters. Patients were ventilated to normocapnia (35-45 mmHg) with 50% to 100% oxygen. Conventional parameters including heart rate, continuous arterial pressure, central venous pressure, and urine output were used for hemodynamic and fluid management. To maintain intraoperative intravascular volume, intraoperative fluid replacement was conducted using continuous infusions of crystalloid solution (Hartmann solution; JW Pharmaceutical, Seoul, Korea, or Plasma Solution A; CJ HealthCare Co., Seoul, Korea) at 4 ml/kg/h as maintenance fluid and additional colloid (Voluven® or Volulyte®; Fresenius Kabi, Bad Homburg, Germany) or crystalloid solution based on the patient’s intravascular volume status according to the preference of the attending anesthesiologists. To maintain mean arterial blood pressure between 65 mmHg and 90 mmHg intravenous fluid replacements was performed, firstly. Nevertheless, if the mean blood pressure was kept below 65 mmHg, vasopressor or inotropic agents were administered: bolus injection of phenylephrine (50-100 μg), ephedrine (5-10 mg) or continuous infusion of norepinephrine, dopamine or dobutamine. Transfusion of packed red blood cells was targeted hemoglobin values above 8 g/dl in patients without history of coronary or cerebral artery disease. If with those histories, the targeted hemoglobin level was 10 g/dl. For the pain control, thoracic epidural catheter was inserted before thoracotomy and patient-controlled analgesia with sufentanil started 5 minutes before the end of surgery. If the insertion of thoracic epidural catheter would not be available due to various reasons, pain control was performed intravenously with fentanyl. After surgery, all patients were transferred to the intensive care unit and discharged to the general ward when their clinical status became stabilized and further intensive monitoring and care were not required.

2. The outcome of esophageal surgery is related to the amount of blood loss and the duration of operation. The authors should include the two factors into the variables of analysis.
Response: Thank you for your important comment. We absolutely agree with reviewer’s opinion that the amount of blood loss and the duration of operation can be associated with postoperative outcomes and should be included in analysis. Therefore, as shown in Table 3 and Table S1 (Additional file), the duration of operation was included in final models. However, in this study, we did not adjust for the amount of blood loss. Although operative blood loss is used to guide perioperative care and is considered as an important prognostic factor, there is, to date, no reliable and accurate method to quantify blood loss during surgery. Indeed, several studies suggested that the current practice of estimating blood loss may be inaccurate and may not be a reliable means to dictate postoperative patient care decisions or to judge physician performance or patient outcomes (Rothermel LD and Lipman JM. Estimation of blood loss is inaccurate and unreliable. Surgery 2016 Oct;160(4):946-953). Therefore, in this study, we used the pRBC transfused intraoperatively as a surrogate parameter for blood loss and included pRBC into the variable of final model (Table 3 and Table S1).

3. The operative methods should be also described in results section.

Response: As recommended, we added the following paragraphs to Result section.

Page 7, Line 14

Among the 892 patients, Ivor Lewis operation, McKeown operation, and salvage esophagectomy were performed in 487 (54.6%), 318 (35.7%), and 87 (9.7%) patients, respectively.

To Reviewer #3:

Torben Glatz, MD (Reviewer 3): I read with interest the study "Effect of restrictive fluid therapy with hydroxyethyl starch during esophagectomy on postoperative outcomes: a retrospective cohort study". While I believe that the authors address an important topic, the study design is unfortunately not suitable to give adequate answers. In this retrospective study the patients receiving intraoperative HES are the patients with intraoperative circulation problems. They are prone to develop postoperative complications. The administration of HES is merely a confounder. I suggest a different study design to investigate this interesting topic.

Response: We greatly appreciate your thoughtful comments. We absolutely agree with reviewer’s opinion that the observed relationship between HES administration and postoperative complications may be confounded by indication. As the reviewer pointed out, it is likely that more HES may have been administered to hemodynamically unstable patients (especially due to
blood loss), and more doses may have been used for these patients. Thus, to reduce confounding by indication, inclusion of intraoperative hemodynamic variables in statistical model should need to be considered. However, unfortunately we could not obtain intraoperative hemodynamic variables in the current study. Therefore, we cannot exactly state whether and to what extent confounding by indication affect our results.

However, in this cohort, additional colloid or crystalloid solution to maintain intraoperative intravascular volume have been given according to the preference of the attending anesthesiologists, and we adjusted for intraoperative use of pRBC which may be a valid surrogate for intraoperative blood loss or hemodynamic instability. Therefore, we do not think that the observed relationship in our study arises entirely from the consequences of confounding by indication.

And we added the following paragraph to Limitations section.

Page 11, Line 4

There were several limitations to our study. First, due to the retrospective nature of our current analyses, our findings should be regarded as a hypothesis generation step, and a causal relationship between the perioperative administration of HES and risk of postoperative complications could not be determined. Although we conducted a multivariable analysis with many variables to obtain reliable results, we cannot exclude some hidden or unmeasured factors that might influence the results. Additionally, we cannot exclude the possibility that the observed relationship between HES administration and postoperative complications may be confounded by indication. In other words, there is a possibility that more HES may have been administered to hemodynamically unstable patients. However, unfortunately, we did not include intraoperative hemodynamic data in our analysis, so we cannot exactly state whether and to what extent confounding by indication affects our results. Thus, our results should be interpreted with caution.

To Reviewer #4:

Ines Gockel, M.D., MBA (Reviewer 4): The paper is well written and the topic is very interesting. However, as retrospective data are available only, the authors should discuss the data and draw the conclusions more carefully. The number of tables could be shortened, however. Without prospective randomized data, no real recommendations can be provided.

Response: We greatly appreciate your thoughtful comments. We absolutely agree with reviewer’s opinion that, because of the retrospective nature of our analyses, our findings should be regarded as a hypothesis generation step and the conclusions must be drawn carefully.
As recommended, we revised as follows and reduced the number of tables.

Page 10, Line 11
Considering these findings, in our present study, the main cause of perioperative AKI in esophagectomy might be due to the use of HES and not restrictive fluid management itself, and the overall rate of morbidity is likely to be influenced by AKI.

Page 11, Line 4
There were several limitations to our study. First, due to the retrospective nature of our current analyses, our findings should be regarded as a hypothesis generation step, and a causal relationship between the perioperative administration of HES and risk of postoperative complications could not be determined. Although we conducted a multivariable analysis with many variables to obtain reliable results, we cannot exclude some hidden or unmeasured factors that might influence the results.

Page 12, Line 11
In conclusion, although intravenous HES administration reduces the total amount of fluid infused during esophageal surgery for esophageal cancer, was associated with an increased risk of postoperative composite complications. Therefore, the administration of HES to achieve a negative fluid balance with restrictive fluid management during esophageal surgery may need to be done very carefully.