Author’s response to reviews

Title: Clinical outcomes of over-the-scope-clip system for the treatment of acute upper non-variceal gastrointestinal bleeding: a systematic review and meta-analysis

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Version: 1 Date: 17 Nov 2019

Author’s response to reviews:

Dear Editors,

Thank you very much for considering publication of our manuscript. The reviewers have made great comments on our manuscript. After discussion with all the co-authors, we revised this manuscript seriously and carefully according to reviewers’ opinions, and highlight the changes to our manuscript by using the track changes mode in MS Word. The answers to each reviewer are as follows:

Respond to Reviewer 1’ comments:
1. Please provide an explicit statement regarding participants, interventions, comparisons, and outcomes (PICO) for this topic.
Answer to question 1: Thank you very much for this suggestion. We added the following sentences “This meta-analysis was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. For this topic, the participants were the patients with acute upper non-variceal gastrointestinal bleeding, the intervention was a treatment method of OTSC, and the outcome was the success rate” in the 1st paragraph of Materials and methods part (Page 3). Because there was no comparison group in our enrolled studies, we didn’t list the controlled group.

2. Did this manuscript have systematic review registration number?
3. Please provide search strategy. Whether did the authors use MeSH terms and All Fields to search gastrointestinal bleeding and OTSC? Whether did the authors use "gastrointestinal hemorrhage," "hematemesis," "melena," or "peptic ulcer hemorrhage" to search the relevant studies?

Answer to question 3: Thanks for this comment. We are so sorry that we didn’t provide search strategy. In our study, we have already used MeSH terms and All Fields to search gastrointestinal bleeding and OTSC, and used "gastrointestinal hemorrhage," "hematemesis," "melena," or "peptic ulcer hemorrhage" to search the relevant studies. Now we have already supplemented search strategy in our study and added that in Table S1. We deleted the sentences “The search terms included ‘gastrointestinal bleeding’ AND ‘OTSC OR over the scope clip’” in 2nd paragraph of Abstract (Page 2). And we changed the sentences ‘Studies published in PubMed, Embase and Cochrane library from January 2007 to May 2019 was searched systematically using the following search terms, ‘gastrointestinal bleeding’ AND ‘OTSC OR over the scope clip’” into “Studies published in PubMed, Embase and Cochrane library from January 2007 to May 2019 was searched systematically using the following search terms, ‘OTSC system’, ‘over the scope clip’, ‘OVESCO’, ‘gastrointestinal bleeding’, ‘ulcer bleeding’, ‘melena’, ‘hemorrhage’ ‘hemostasis’ and others. The terms were used in all possible combinations to obtain the maximal number of articles. Table S1 showed the search strategy of each of search engines."

4. Whether were "OTSC" and "over the scope clip" enough to search the relevant studies?

Answer to question 4: Thanks for this suggestion. To make our search strategy more comprehensive, we also used other terms, such as ‘OTSC system’ and ‘OVESCO’, which were shown in Table S1. After that, the study flowchart changed, but the number of enrolled studies in our final analysis was still sixteen. We already revised the Figure 1 in our manuscript.

5. Figure 2 showed the proportion of acute upper non-variceal gastrointestinal bleeding etiologies. The etiologies are various. The risks of recurrent bleeding are different between these etiologies. For the concern of risk of bias, whether was the population that was intended to be sampled representative?

Answer to question 5: We agreed with this point. The purpose of Figure 2 was to show the etiologies proportion of the included studies. Some included studies were missing data for our review variables of interest, such as treatment outcome for each patient. Through repeatedly reviewed the full text and contacted the author by email, the data still can not be obtained. So we can’t conduct subgroup analysis to analysis the clinical outcomes of OTSC for different etiologies of bleeding. The above have been written in the 10th paragraph of Discussion (Page 10). We also added the following sentences “We could not get the data of the individual patient, which would allow us to perform more detailed analysis, such as subgroup analysis of OTSC for different etiologies of bleeding.” in the 10th paragraph of Discussion.

6. Regarding "Criteria for inclusion and exclusion" (Page 4), the authors reported that "Re-bleeding was diagnosed if a retreatment of the target lesion was required after initial successful endoscopic treatment." It is different from what we know about the definition of re-bleeding. In
fact, clinical re-bleeding is diagnosed if persistent tarry stool passage with tachycardia, shock, or the hemoglobin level drop. Please explain why the authors made the definition.

Answer to question 6: Thanks for this comment. We agreed with this point. After repeated reviewed our included studies, re-bleeding was defined as development of fresh hematemesis, melena, hematochezia, shock, or a drop in hemoglobin of more than 2 g/dL within 24 hours [1-3]. So we change the sentences “Re-bleeding was diagnosed if a retreatment of the target lesion was required after initial successful endoscopic treatment” into “Re-bleeding was defined as development of fresh hematemesis, melena, hematochezia, shock, or a drop in hemoglobin of more than 2 g/dL within 24 hour, with need for repeat treatment” in the Criteria for inclusion and exclusion part (Page 4).

References

Respond to Reviewer 2’ comments:
1. In this field, there several similar articles had talked about this issue. (1-3) The author's conclusion was like other publish papers but their inclusion articles and patients was much more. Authors may consider search again for find more studies.

Answer to question 1: Thanks for this comment. Weiland et al.’s [1] studies aimed to evaluate the effectiveness and safety of the OTSC system for the gastrointestinal hemorrhage, acute leaks/perforations, and chronic leaks/fistulae. Kobara et al.’s [2] clarifies the current status and limitations of OTSC according to different indications of GI refractory disease, including refractory bleeding, perforation, fistula, anastomotic dehiscence. Chandrasekar et al.’s [3] aimed to evaluate the effectiveness and safety of the OTSC system for gastrointestinal bleeding. But in our study, we aimed to conduct a systematic review to evaluate the effectiveness and safety of the OTSC system for management of acute non-variceal upper GI bleeding, which is different from the above 3 published papers. Because our study just limited to the acute non-variceal upper GI bleeding, the number of inclusion articles and patients was less than these three studies. We already added some more search terms, such as ‘OTSC system’ and ‘OVESCO’, shown in Table S1, but the number of enrolled studies in our final analysis was still sixteen.

References
2. Since OTSCs is invasive procedure, the adverse events post OTSCs may need further considered. Such as perforation or obstruction after OTSCs and some papers had mentions these adverse events.

Answer to question 2: Thanks for this comment. As you suggested, we already mentioned the adverse events, such as perforation and obstruction in our paper in discussion part (4th paragraph, Page 9). Albert et al. [1] reported one case was perforation and Richter-Schrag et al. [2] Reported one case was obstruction. In addition, we also mentioned that there were other OTSC-related complications reported in some studies [3-6] when OTSC was applied for closure GI perforation or fistula, such as esophageal perforation, acute cholangitis, inadvertent tongue piercing and jejunal stenosis.

References

3. If possible, may consider add subgroup analysis in studies to identified some parameters effect in the OTSC treatment in UNVGIB (such as lesion characteristics, study location, study times….)

Answer to question 3: Thank you very much for this suggestion. We added subgroup analysis to identify whether the study times and study sample size effect the result of the OTSC treatment in UNVGIB in our manuscript (Figure 5 and 6). We added the following sentences “We also conducted subgroup analysis to identify the effect of study period and study sample size in the OTSC treatment in UNVGIB. Nine studies (n = 218) were published between 2011 and 2016, while 7 studies (n = 560) were published between 2017 and 2019. Subgroup analysis showed the clinical success rate was 86.5% (95%CI, 80.7%-90.7%) and 82.3% (95%CI, 70.3%-90.1%).
respectively (Figure 5). The number of studies with less than 30 patients or those with greater than or equal to 30 patients was same (n = 8). Subgroup analysis showed the clinical success rate was 79.9% (95%CI, 69.9%-87.3%) and 86.6% (95%CI, 76.6%-91.6%), respectively (Figure 6).” in Clinical outcomes of Result part (Page 6). Because the studies we included were small sample and some important data were missed, we can’t conduct other subgroup analysis to identified parameters effect in the OTSC treatment in UNVGIB, such as lesion characteristics, study location and so on.

In addition to correct this manuscript according to the reviewers’ advice, we also checked the manuscript time and time again to avoid grammatical or spelling errors throughout the article. Hope our corrected manuscript can be published in your journal soon. That will be our great honor.

Thank you very much! Best wishes!

yours sincerely,

Xiaowei Tang