ANSWERING REVIEWERS

April 7th, 2019

Dear Editor,

Please find enclosed the edited manuscript in word format (file name: 46415-Manuscript-File-revision.docx)

Title: Carvedilol versus endoscopic variceal ligation for primary and secondary prevention of variceal bleeding: systematic review and meta-analysis

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On behalf of all authors, I would like to thank reviewer 1 and 2 for his/her kind review on our manuscript. The manuscript has been improved according to the suggestions of reviewers:

Reviewer 1 (ID: 03478568)
The topic deserves clinical practice, and is different to our traditional guideline. However, there are some details to be discussed, as described in the comments. I would like to learn what the authors explain for these comments.

Comment #1:
The time span should be prolonged to include more clinic trials.

Response :
We agree with the reviewer that with longer time span of literature searching, more trials might be added to our study. Unfortunately, considering the working capacity of each authors, we initially set six months as the maximum time span for literature searching. On the other hand, we have also searched for potential studies in clinical trial registries such as in clinicaltrials.gov and World Health Organization International Clinical Trials Registry Platform (WHOICTRP). Unfortunately, the status of one potential clinical trial was 'withdrawn' and another trial was still in recruitment process until the next following year. Thus, we decided to finish the literature searching and only included our present studies.

Comment #2:
The etiology and severity could remarkably impact the medical decision and the outcome of this kind of disease.

Response :
We thank the reviewer for this detail comment. We cannot completely agree with the reviewer on this issue. In terms of the impact of cirrhosis etiology, we have not found any literature that mentioned any correlation between etiology and the outcome of esophageal varices. In terms of disease severity of

cirrhosis (measured by Child Pugh score) and grade or size of varices, it is very reasonable to think that different study population may have different outcome of disease. We tried to test the consistency of each result by conducting subgroup analysis. Unfortunately, most of the included studies did not perform specific analysis for different group of Child Pugh score. We also could not retrieve complete data about the size or grade of varices in some of the studies. Therefore, we add this as a limitation of our study as follow:

"There are several limitations in this systematic review and meta-analysis that bear mentioning. First, we could not retrieve complete data from some included studies which hindered us to do some subgroup analysis, such as subgroup analysis of cirrhosis severity or numbers of EVL procedure performed. Most of the included studies also did not perform specific analysis regarding this particular topic. Second, the numbers of available clinical trials are relatively limited which also hindered us to perform sensitivity analysis for this study."

Comment #3:
The mortality should definitely result from variceal bleeding because there are some other causes leading to death in patients with liver cirrhosis.

Response :
We agree with the reviewer with this issue. From the beginning, we have already specified that our primary outcomes for mortality in this study are bleeding-related mortality and all-cause mortality. Those two outcomes should be measured separately to ensure the validity of outcome measurement of each intervention. We still wanted to measure the all-cause mortality because based previous literatures, it may be affected by the therapeutic effect of beta blockers.

Comment #4:
"A significant difference in overall mortality, bleeding-related mortality, and upper gastrointestinal bleeding between patients treated with carvedilol or EVL to prevent first variceal hemorrhage was not seen in a previous systematic review. However, only two studies were included in the review, and a statistical comparison was not performed for secondary prevention."

The conclusion of the secondary prevention seems unreasonable. Why not exclude this condition?

Response :
Based on your response, we consider that our sentence may be ambiguous and may be easily misinterpreted. We revised that sentence into this following sentence :

"A significant difference in overall mortality, bleeding-related mortality, and upper gastrointestinal bleeding between patients treated with carvedilol or EVL to prevent first variceal hemorrhage was not seen in a previous systematic review. However, only two primary prevention studies were included in the review. On the other hand, until present, there is no systematic review or meta-analysis comparing carvedilol with EVL for the secondary prevention of variceal bleeding."

Comment #5:
"We hypothesized that carvedilol could be used to prevent primary and secondary variceal bleeding in patients with cirrhosis in hospitals that are unable to offer EVL."

The hypothesis focused on economic and social factors but not the maximum benefit the patients.

Response :

Some of the major drawbacks of EVL are invasive, costly, and unavailable in many areas, especially in developing countries. We agree with the reviewer that our hypothesis statement should be revised to translate our assumption that carvedilol may also benefit cirrhotic patients in general. Therefore, we adjusted our hypothesis statement as follow:

"We hypothesized that there was no difference between carvedilol and EVL intervention for primary and secondary prevention of variceal bleeding in cirrhosis patients. In many developing countries, EVL intervention is only available at specific secondary or tertiary healthcare centres. We presumed that carvedilol may be the best prevention strategy of variceal bleeding, especially in hospitals that are unable to offer EVL."

Comment #6:
"Our initial intention was to perform sensitivity analysis of heterogeneity found in the pooled studies through the exclusion of studies with low-quality results. However, this did not occur owing to a paucity of data. Subgroup analysis was conducted of the primary bleeding outcomes based on the grade of varices."

The multiple times EVL treatment could affect the outcome, which should be considered.

Response :
We thank reviewer #1 for his/her comment on this. We agree that the number or frequency of EVL procedure may also affect the outcome and subgroup analysis for this particular condition should have been planned beforehand and this will be a constructive feedback for our upcoming projects. We have reviewed the possibility of performing the subgroup analysis on the frequency of EVL, but it might not be appropriate since the frequency of EVL on every studies are still in between the range of recommended dose (every 2-8 weeks). Most studies used EVL every two weeks as standard of intervention. Only one study used EVL in every 3 weeks and one study did not mention the frequency of EVL intervention. We have added this issue in the limitation section as mentioned in response to comment #2.

Reviewer 2 (ID: 02541391)
The manuscript "Carvedilol vs. EVL for primary and secondary prevention of variceal bleeding" is well-written, in a concise language. The title reflects the major topic and contents of the manuscript. I consider that the article is suitable for publication after revising the language and grammar. However, I would recommend a more cautious formulation of the concluding remark.

Response :
We thank reviewer #2 for this comment on our conclusion. We revised our conclusion as follow:

"Carvedilol had similar efficacy to EVL in preventing the first variceal bleeding in cirrhosis patients with esophageal varices. We considered that carvedilol was superior to EVL alone for secondary prevention of variceal bleeding in regard to all-cause mortality reduction."

Thank you again for considering our manuscript for publication in the *World Journal of Hepatology.*

Sincerely yours,
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