

Name of journal: World Journal of Hepatology

Manuscript NO: 69584

Title: Effects and safety of natriuretic peptides as treatment of cirrhotic ascites: A systematic review and meta-analysis

Dear Editors

Thank you for the swift and positive handling of our manuscript. We also wish to thank the reviewer for his/her relevant and constructive comments.

Please find below in italic our responses to each issue raised in the peer-review report.

We have adjusted the manuscript accordingly and believe that the manuscript has improved during the editorial process. We have submitted a version of the manuscript with track-changes.

We hope that you will find the revised manuscript suitable for publication.

Sincerely,

Rasmus Hvidbjerg Gantzel

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: WJH-69584 Gantzel RH et al. Effects and safety of natriuretic peptides as treatment of cirrhotic ascites: A systematic review and meta-analysis. In this review article, Gantzel et al performed a meta-analysis which examined the effects and safety of applying natriuretic peptides to cirrhosis patients with ascites. They found that sodium excretion increased in response to continuous ANP infusion and was more pronounced when infusion rates of >30 ng/kg/min were applied. Moreover, natriuresis was significantly higher in those with mild/moderate ascites compared with moderate/severe and refractory ascites. The study design, statistical analyses and discussion are appropriate.

- *We are grateful for the kind evaluation of our manuscript.*

However, there are some issues to be clarified: Major comments

1. The authors identified that first, plasma aldosterone concentration and renin activity were significantly elevated at baseline in study subgroups achieving a negative sodium balance in response to an ANP administration compared with treatment non-responders ($p < 0.01$). The second finding is that subgroups with mild/moderate ascites have the most pronounced ANP natriuretic response than that with refractory ascites. It has been known that patients with refractory ascites have a more prominent activation of renin-angiotensin-aldosterone axis and higher aldosterone levels. This makes the two findings contradictory. Please provide the readers more information by summarizing the discussions on this point from the analysed studies or discussing the underlying mechanism.

- *Thank you for this highly relevant remark concerning a particularly interesting finding. In the subgroup analysis regarding plasma aldosterone concentrations and renin activity, we found that baseline concentrations of these hormones were significantly lower in study subgroups that achieved a negative sodium balance on intervention (the responders) compared with non-responder study subgroups. We identified that baseline concentrations of plasma aldosterone concentrations and renin activity were significantly higher in subgroups with refractory ascites compared with non-refractory ascites. In accordance with these findings, subgroups with mild/moderate ascites had higher baseline and peak sodium excretion compared with refractory ascites subgroups. This is described and illustrated in the abstract, result section, Figure 5, and Figure 6 of the revised manuscript.*

2. The serum sodium and potassium levels can be affected by ANP and affect the cirrhotic patients with ascites significantly. Did the analysed studies collect the sodium and potassium levels in response to ANP administration?

- *This is indeed an interesting question. Since the serum sodium and serum potassium were not included in our PICO, we refrained from collecting these details from the references. However, we have now searched the references, and Table 1 have been updated (added baseline sodium for Morali et al, 1991). Baseline serum sodium was measured in nine of the included studies covering 12 study subgroups, and in only one of these studies a serum sodium concentration after ANP administration was provided, which was unchanged from baseline.*

The baseline serum sodium generally reflected the disease severity, with the lowest concentrations in study subgroups characterised by refractory ascites. Baseline serum potassium concentration was measured in four studies covering six study subgroups, without any measurements after ANP infusion. The serum potassium concentrations in these six study subgroups were largely similar (range: 3.7 – 4.4 mmol/L). These details are now included in the discussion section of the revised manuscript.

Science editor:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Specific Comments to Authors: The manuscript elaborated a study of the Effects and safety of natriuretic peptides as treatment of cirrhotic ascites. It is unacceptable to have more than 3 references from the same journal. To resolve this issue and move forward in the peer-review/publication process, please revise your reference list accordingly.

- *We thank the scientific editor for the relevant comments to our manuscript. We agree that multiple references from the same journal, in general, must be avoided. However, since the present study is a systematic review, it would be scientifically wrong to exclude any of the references identified through the database search solely due to this criteria. In your Format-example of Meta-analysis (Title: Outcomes of robotic vs laparoscopic hepatectomy: A systematic review and meta-analysis), "Annals of surgery" is referred to seven times and "Surgery Endoscopy" receives nine citations. However, we have went through the reference list and removed unnecessary references from the introduction.*

The author should clarify the inclusion criteria and exclusion criteria of the study.

- *The inclusion criteria are described in the Materials and Methods section. Reasons for exclusion are provided in the Figure 1.*

Most of the studies included by the author were before 2000, which has a great impact on the research value and reference significance of this study.

- *We thank the reviewer for this highly relevant comment. We are aware, that the causes for cirrhosis have changed during the past three decades, in particular due to a decreased burden of hepatitis C virus infection and increased frequency of metabolic liver disease driving the*

development of cirrhosis. However, we here focus on cirrhosis decompensation with ascites, which occurs late in the disease course, and the underlying aetiology may be less important at this stage. We discuss this concern on page 18 of the revised manuscript. For the 243 patients included in this systematic review, the cirrhosis aetiology was provided for 185. 131 (71%) had alcohol-related cirrhosis, 23 (12%) had cirrhosis due to chronic infection with either hepatitis C or B virus, 18 (10%) were characterized as cryptogenic cirrhosis, and 13 (7%) had cirrhosis from other aetiologies. This data is provided in the Supporting Information. 20 years ago metabolic-associated cirrhosis was rarely recognized, and we may assume that some of the patients with cryptogenic cirrhosis were misdiagnosed patients with metabolic-associated disease. If we include that assumption, the distribution of aetiologies in these studies is not much different from today, allowing translation of our results to the present.

Company editor-in-chief:

Specific Comments to Authors: I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Hepatology, and the manuscript is conditionally accepted.

- *We are thankful for this generous decision by the company editor-in-chief.*

I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

- *Please find two separate PowerPoint files included with the resubmission. One includes the figures for the manuscript and the other includes all figures presented in the Supporting Information.*

Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or

column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

- *All tables are now provided as standard three-line tables. Moreover, the revised manuscript has been updated with the Article Highlights section.*