ANSWERING REVIEWERS

June 12, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 11358-review.doc).

Title: Effects of neutrophil elastase inhibitor in patients undergoing esophagectomy: A systematic review and meta-analysis

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 11358

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reviewer #1:

Dear authors, this is a nicely written manuscript with a thouroughly performed review and meta analysis on the use of sivelestat perioperatively for esophagectomy.

(1)Comments: In general there seems to be a risk of interpretation in favor of Sivelestat. At several occasions the data is interpreted in favor of Sivelestat despite unsignificant differences between the study groups. On the other hand, unsignificant differences in complications are interpreted as "no difference". Please be advised to read the paper of Dougman et al. "Absence of evidence is not evidence of absence" and to be more careful with the interpretation of your very nice results and very thouroughly performed data analysis.

Response: We thank you very much for the advised paper. We have carefully read the paper, and the interpretation was improved according to your kind comments.

(2)Comments: In the SIRS and postoperative hospital stay sections it remains unclear to me how the studies were selected to be included in the pooled analysis.

Response: Studies were selected mainly according to wether the study reported the detailed data. In the SIRS section, a total of five studies presented detailed data, which contained two parts(data can

be pooled in qualitative meta-analysis, n=0; data can be pooled in quantitative meta-analysis, n=5). Similarly, in the postoperative hospital stay section, a total of four studies presented detailed data, which contained two parts(data can be pooled in qualitative meta-analysis, n=2; data can be pooled in quantitative meta-analysis, n=2).

(3)Comments: In the SIRS section the authors write "the difference failed to reach statistical significance (p=0.048)"? Is there an error?

Response: We are very sorry for incorrect writing the number of studies which reported significant or unsignificant difference in terms of SIRS. This error in the SIRS section was corrected and was marked in red.

(4)Comments: In the discussions section the authors state there were different surgical procedures used, such as open surgical as well as minimally invasive esophagectomy. The procedures used in the different studies are specified in table 2. The surgical procedures should be clarified in terms of open vs. minimally invasive approaches, as well as for abdominal vs. thoracic, cervical and combined approaches.

Response: As stated in the Discussion, different surgical procedures were adopted in the included studies, and the surgical procedures really should be clarified. While we found it hard to obtain comprehensive and sufficient information from the surgical procedure section in the included studies. But as stated the intervention was comparable between sivelestat and control group in each included study, this difference might not raise concerns.

(5)Comments: Neoadjuvant treatment should also be specified for all studies in table 2. The blood loss in the saline group of Kawah et al. in table 2 is given as 32 with a range of 150-1910, this must be an error?

Response: We accepted your kind comments. While, when we tried to specify the neoadjuvant treatment, we found it was hard. Sivelestat was mainly used in patients undergoing esophagectomy for protect the surgery stress in a short time, so the papers mainly focus on the peri-operative clinical outcomes. Meanwhile, the adjuvant treatment between groups in each studies was comparable, the authors reported really little information in the included studies. We are very sorry for incorrect writing the blood loss volume in the saline group of Kawah et al in Table 2. The median volume was corrected to 320, as marked in red in the Table 2.

(6)Comments: Table 4 contains only 3 out of 5 studies relevant for the analysis?

Response: We are very sorry about that. The number of qualitative pooled studies which presented available data of duration of mechanical ventilation (n=3), ICU stay(n=3), SIRS(n=5), postoperative hospital stay(n=2) was different, so we choose to present 3 out of 5 studies in the table 4 to obtain a neat typesetting.

(7)Comments: Mechanical ventilation and Figure 2: Concerning duration of ventilation on Day 3 or Day 5: How can the duration of mechanical ventilation be specified on a day? What is this supposed to mean? Was this group given Sivelestat until POD 5? Was the duration of mechanical ventilationmeasured on POD 5? Please specify.

Response: We are very sorry for improper expression. In the included studies, we performed a subgroup analysis according to the Sivelestat administration time (from operation to postoperative day POD 3 or POD 5). We accepted your kind comments, and we specify it in the Mechanical ventilation and Figure 2 section of Result, as marked in red.

(8)Comments: In the discussions section concerning the studies that found no effect of Sivelestat within more invasive open surgical procedures the authors suggest to simply higher the dose of Sivelestat and to reduce the invasiveness of the procedures. There seems to be a lack of evidence for this statement as for now and the authors should be more cautious.

Response: We accepted your kind comments. And we corrected this statement as "Therefore, additional sivelestat administration after the more invasive surgical procedure may lead to little clinical benefits, and the effects of different procedures in addition to higher dose of sivelestat should be investigated in the future", which was marked in red in the Discussion.

(9)Comments: Discussion: Please be more cautious with the interpretation of the nonsignificant differences. These should only be seen as possible but not definitive effects.

Response: Of the reported result, ICU stay time and postoperative hospital stay was decreased in the sivelestat group compared with control group, but both of them failed to reach significant differences. We accepted your comments, and the interpretations were revised as marked in red.

(10)Comments: Discussion: "It was found that with the mechanical ventilation support, pulmonary

complications and SIRS were improved..." Is this sentence complete??

Response: We are very sorry for incorrect writing the sentence. It was corrected as "It was found that with sivelestat administrated after operation, the mechanical ventilation support, pulmonary complications and SIRS were improved, but the ICU stay and postoperative hospital stay were not significantly shortened."

(11)Comments: Discussion: Possible explanations for the findings: The absence of a Sivelestat effect should also be discussed!

Response: We accepted your kind comments. And the absence of a sivelestat effect was discussed in the Discussion section and was marked in red.

(12)Comments: The interpretation of the available data on methylprednisolone administration are different in the beginning and end of the discussion.

Response: We are very sorry about that. And the statement of methylprednisolone administration was deleted.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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