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*Retrospective Study*

**Oral esomeprazole versus injectable omeprazole for the prevention of hemorrhage after ESD**

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**Responses to Reviewer 03474116's comments**

Thank you very much for your valuable and constructive comments regarding our manuscript. We believe that your comments have significantly improved the revised manuscript.

Our responses to your comments are as follows:

1. Previously, size of gastric cancer, location, histology, kind of gastric acid suppressants, dialysis and long procedure time are reported to associate with the post-ESD gastrointestinal bleeding. Why did authors fail to show possible factors? How about dialysis patients?

Our response

Thank you for this comment. We mentioned the possible factors in Table 1, and Page 10, Line 13 in the revised manuscript. No dialysis patient underwent ESD during the study period. Previous studies have reported the incidence and risk factors for hemorrhage after ESD, although the results are conflicting. We consider that the discrepant results are due to the diversity of the ESD procedures and treatments used.

2. When ESD was performed, antiplatelet/anticoagulant drugs might be stopped. Authors should show whether antiplatelet and/or anticoagulant drugs were stopped. In addition, a risk of intake of antiplatelet and anticoagulant drugs for bleeding differs.

Our response

Thank you for this comment. Antiplatelet/anticoagulant drugs were discontinued before the ESD. We have mentioned this in Page 6, Line 15 in the revised manuscript. Unfortunately, in this study, we did not consider antiplatelet and anticoagulant drugs separately.

3. In general, oral PPI od therapy did not increase intragastric pH at maximum level during 3-5 days. However, intravenous PPI bid therapy increase intragastric pH at 2 days. This observation may suggest that potent acid inhibition after ESD did not require during 1-3 days. In addition, authors should revise Discussion section about associations with intragastric pH and PPI administration.

Our response

Thank you for this comment. Recently, Laine et al. <sup>[26]</sup> and Javid et al. <sup>[27]</sup> demonstrated that a similar intragastric pH can be achieved by oral PPI and IV PPI. Based on this evidence, some studies have reported that oral EPZ therapy is a useful alternative to injectable PPI therapy to prevent recurrent hemorrhage in patients with hemorrhagic gastric ulcer <sup>[24, 25]</sup>. We have mentioned this in Page 10, Line 1 in the revised manuscript.

4. Why did authors compared with intravenous omeprazole and oral esomeprazole, not oral omeprazole?

Our response

Thank you for this comment. Unfortunately injectable esomeprazole is not available at present in Japan. Oral esomeprazole is expected to be more beneficial than oral omeprazole, thus, we compared intravenous omeprazole with oral esomeprazole in this study.

5. How about CYP2C19 genotypes?
7. There was no significant difference in bleeding rate after ESD between esomeprazole and omeprazole. Sulfate may offset difference of intragastric pH.
8. Kind of acid suppressant may affect rate of scar formation at 35 days post ESD.

Our response

Thank you for this comment 5, 7 and 8. Unfortunately there have been no such studies.

6. No statistically significant difference was seen between these groups (EPZ group vs.

OPZ group; OR, 0.89; 95% CI, 0.35-2.27; P = 1.00). Is the p value is right?

Our response

Thank you for this comment. Statistical analysis was carried out again, and p value was the same.

9. Please add data all patients in Table 1.

Our response

Thank you for this comment. We have attached the data as supplemental material.

**Responces to Reviewer 03475590's comments**

Thank you very much for your valuable and constructive comments regarding our manuscript. We believe that your commnts have significantly improved therevised manuscript.

Our responces to your comments are as follows:

1. I advise authors to conduct a study about oral esomeprazole (EPZ) versus injectable esomeprazole (EPZ) therapy to prevent hemorrhage after ESD.

Our response

Thank you for this comment. Unfortunately injectable esomeprazole is not available at present in Japan. We would like to consider it when it becomes available.

**Responces to Reviewer 03002202's comments**

Thank you very much for your valuable and constructive comments regarding our manuscript. We believe that your commnts have significantly improved therevised manuscript.

Our responces to your comments are as follows:

1. I wonder, why omeprazole oral and intravenous was not compared and you have chosen different PPIs. But I believe that the results of this study might be useful in clinical practice.

Our response

Thank you for this comment. Unfortunately injectable esomeprazole is not available at present in Japan. Oral esomeprazole is considered to be more beneficial to patients than omeprazole; therefore, we compared intravenous omeprazole with oral esomeprazole in this study.

Thank you very much. We believe that the revised manuscript is significantly improved because of your comments. We hope that the revised manuscript is acceptable for publication in *World Journal of Gastrointestinal Endoscopy*.