Format for ANSWERING REVIEWERS

June 4, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name:10677WJGRevised).

Title: Two-week treatment with PPI is sufficient for healing post ESD ulcers

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Thank you for your e-mail, on our paper titled "Two-week treatment with PPI is sufficient for healing post ESD ulcers". Format and references and typesetting were corrected. The following are our responses and changes that we made in keeping with the comments of the reviewer.
We look forward to hearing from you at your earliest convenience.

Sincerely yours,

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Reviewer 00503623

This is an interesting and well presented report clearly demonstrating that 2-week regimen of PPI treatment of patients with ESD ulcers is as efficacious a the commonly employed 4-week regimen. Good job !

Thank you for your comment.

Reviewer 00036517

1. **This ulceration after ESD is not similar to H. pylori infected ulceration. So, I suggest that authors need to compare the difference in ulcer healing between 2 weeks and 4 weeks of PPI administration in H. pylori infected patients.**

Thank you for your nice comment. We also agree that ulceration after ESD is not similar to H. pylori infected ulceration. Therefore, we tried to shorten the duration of PPI treatment after ESD and we do not intend to shorten it in peptic ulcer related to H.pylori infection. It is impossible to identify the occurrence timing of *H. pylori* infected ulcer and judge which *H. pylori* infected ulcer is deteriorating or recovering, on the contrary, the occurrence timing of the artificial ulcer after ESD can be identified easily. Thus, it is very difficult to compare the difference between the *H. pylori* infected ulcer and the artificial ulcer after ESD directly. In accordance with reviewer's comment, we changed as follows:

(Introduction, p5 line 5 from the bottom)

…It is difficult to identify the occurrence timing of peptic ulcers associated with *Helicobacter pylori* (*Hp*) infection accurately and to compare the difference in ulcer healing between the *Hp* infected ulcer and the artificial ulcer after ESD directly. In contrast, Hashimoto et al. reported that the speed of healing of artificial ulcers was faster than that of ordinary peptic ulcers (9, 10) and showed that the pathophysiology of artificial ulcers which form after ESD might differ from peptic ulcers associated with *Hp* infection. Therefore, we suppose that the duration of PPI treatment for post ESD ulcers might be reduced to avoid the side effects of PPIs, unlike peptic ulcers associated with *Hp* infection.

2. **(a) The number of patients in this study is small. I wonder if the reason for no-difference between the 2 groups is influenced by the number of the patients. I suggest that authors need to add more patients. (b) The authors excluded 4 patients due to the size of the ulcer but the reason for these exclusions is not clear. Including these patients in the study might have altered the results perhaps these would have been a significant difference in the excluded patients.**

(a) Thank you for your comment. It is difficult to estimate the necessary and enough number of patients in the non-inferiority trial statistically. In general, to demonstrate the non-inferiority, the analysis of confidence interval is used widely. So we analyzed our results by comparing the confidence interval of 2W groups with that of 4W. As a result, the average and confidence interval of 2W and 4W groups were 96.1% (95%CI 94.6-97.5) and 94.8% (95%CI 92.6-97.1), respectively, which showed that the confidence interval of 2W is included in that of 4W and the non-inferiority of 2W compared with 4W is proved.

We changed Table 1, Abstract, and Results as follows;

(Abstract)

…The numbers of patients with ulcers in the healing / scar stage in the 2W and 4W groups at 4

weeks after ESD were 20/6 and 28/5, respectively, with no significant difference. For patients with ulcers in the healing stage at 4 weeks, the ulcer healing rate in the 2W and 4W groups were 96.1% (95% Confidence interval [CI] 94.6-97.5) vs. 94.8% (95%CI 92.6-97.1), respectively, with no statistical difference (UMIN000006951).

(Results, p9, line 2)

…The clinical characteristics of the 60 patients after ESD treatment are shown in Table 1 and the average size of ESD in the 2W group was less than that of the 4W group (p = 0.048, Mann-Whitney U test) in spite of randomized assignation.

(Results, p 9, line 9)

…The numbers of patients in the ulcer healing (H) / scar (S) stage at 4 weeks after ESD were 20/6 and 28/5 in the 2W and 4W groups, respectively, and this showed no significant difference (Table 1). There was no ulcer in the active stage. We evaluated the ulcer healing rate at 4 weeks and these were 96.1 % (95% confidence interval [CI], 94.6-97.5) vs. 94.8 % (95%CI 92.6-97.1), respectively, which showed the non-inferiority of 2 weeks' treatment compared with 4 weeks' one.

(b) One patient showed the re-bleeding within 2 weeks and received endoscopic treatment. Therefore, this patient should be included to intention to intention to treat analysis, as the reviewer pointed. So we corrected Table 1. We performed the analysis again 59 patients and changed results and Table 1. Unfortunately, the size of ESD is different between 2W and 4W groups in spite of randomized assignation, but there was no significant difference in the number of patients with ulcer stages (active / healing / scar) and ulcer healing rate (%) between 2W and 4W groups (Table 1). To adjust for the difference of ESD size between 2W and 4W groups, we selected the patients who were within the range (average ± 1SD), and the size-matched analysis was also performed (Table 3).

(Results, p9 line 1 from the bottom)

…We observed a significant difference between the rapid healing and non-rapid healing groups in the initial ulcer size (p<0.001, Mann-Whitney U test) and the disease rate of hypertension (p = 0.049, chi-square test) (Table 2).

(Result, p10 line 5)

…To adjust for the difference of ESD size between 2W and 4W groups, we selected the patients who were within the range (average ± 1SD), and the size-matched analysis was also performed (Table 3). As a result, there was no significant difference in ulcer healing rate and speed.

3. **In this study, authors treated with PPI and rebamipide. The ulcer healing after ESD was influenced by not only PPI therapy but also rebamipide. For the discussion of the difference between 2 and 4 weeks PPI treatment, I suggest that authors include 2 and 4 weeks PPI therapy without rebamipide administration.**

Thank you for your comment. To ensure the safety of this study in view of reducing the risk of re-bleeding, we used rebamipide. In our previous report, we treated 45 artificial ulcers after ESD only by PPI and showed that the healing rate was 94.6% (95%CI, 90.7-98.5%), which was not different from those of 2W or 4W groups. This result teaches us that the improvement by adding rebamipide is limited. Therfore, we think that adding rebamipide could not change the results in our study. We changed Discussion as follows;

(Disucussion, p13 line10)

…But, in our previous report (23), we treated 45 artificial ulcers after ESD only by PPI (esomeprazole or omeprazole) and showed that the healing rate was 94.6% (95%CI, 90.7-98.5%), which was not different from those of 2W or 4W groups in this study. This result suggested us that the effect on healing ulcer by adding rebamipide was limited.

4. The way the tables are presents these is no clear key to read them, they should be made easier to read.

Thank your for your comment. We brushed up Tables again.

Major point   All Helicobacter pylori and H. pylori should be in italic.

We corrected them.

Reviewer 00068211

1. In the methodology part , All patients received rebamipide 300 mg per day for 4 weeks. For rebamipide is another drug for treating ulcer, it may affects the efficacy of   PPI. So I suggest that authors should remove rebamipide in therapy.

Thank you for your comment. To ensure the safety of this study in view of reducing the risk of re-bleeding, we used rebamipide. In our previous report, we treated 45 artificial ulcers after ESD only by PPI and showed that the healing rate was 94.6% (95%CI, 90.7-98.5%), which was not different from those of 2W or 4W groups. This result teaches us that the improvement by adding rebamipide is limited. Therfore, we think that adding rebamipide could not change the results in our study. We changed Discussion as follows;

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2. In table 1, 2W and 4W has 27 and 33 patients, respectively, but In table 2, the number of patients became 26 and 30. I wonder why the author excluded 4 patients ,and what the exclusion criteria is ?

Thank you for your comment. One patient showed the re-bleeding within 2 weeks and received endoscopic treatment. Therefore, this patient should be included to intention to intention to treat analysis, as the reviewer pointed. So we corrected Table 1. We performed the analysis again 59 patients and changed results and Table 1. Unfortunately, the size of ESD is different between 2W and 4W groups in spite of randomized assignation, but there was no significant difference in the number of patients with ulcer stages (active / healing / scar) and ulcer healing rate (%) between 2W and 4W groups (Table 1). To adjust for the difference of ESD size between 2W and 4W groups, we selected the patients who were within the range (average ± 1SD), and the size-matched analysis was also performed (Table 3).

(Results, p9 line 1 from the bottom)

…We observed a significant difference between the rapid healing and non-rapid healing groups in the initial ulcer size (p<0.001, Mann-Whitney U test) and the disease rate of hypertension (p =

0.049, chi-square test) (Table 2).

(Result, p10 line 5)

…To adjust for the difference of ESD size between 2W and 4W groups, we selected the patients who were within the range (average ± 1SD), and the size-matched analysis was also performed (Table 3). As a result, there was no significant difference in ulcer healing rate and speed.

Reviewer 00068864

Nice article

Thank you for your comment.

Reviewer 00070504

This is an interesting and well presented report.

Thank you for your comment.