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## A Case-Control Study of Esomeprazole Plus Rebamipide vs. Omeprazole Plus Rebamipide on Post-ESD Gastric Ulcers

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### Abstract

**Objectives:** Endoscopic submucosal dissection (ESD) is useful for treating gastric tumors. Several trials have shown the efficacy of 4 or 8 weeks of proton pump inhibitor (PPI) administration for post-ESD ulcers. However, if the size of the post-ESD ulcer is larger than predicted, PPI administration alone might not be sufficient for the ulcer to heal within 4 weeks. There is no report about the efficacy of post-ESD gastric ulcers by esomeprazole. We examined retrospectively the efficacy of a combination therapy of esomeprazole plus rebamipide, a mucosal-protective antiulcer drug, on the acceleration of post-ESD ulcer healing comparing with omeprazole plus rebamipide.

**Methods:** We reviewed the medical records of patients who underwent ESD for gastric neoplasia. We conducted a case-control study to compare the healing rates within 4 weeks effected by esomeprazole plus rebamipide (group E) and omeprazole plus rebamipide (group O). The sizes of the artificial ulcers were divided into normal-sized or large-sized.

**Results:** The baseline characteristics did not differ significantly between the two groups except age and sex. Stage S1 disease was observed in 27.6% and 38.7% of patients after 4 weeks of treatment in the group E and O, respectively. In large-sized artificial ulcers, the healing rate of stage S1 in group E is significantly higher than that in group O in 4 weeks. (25% VS 0%:  $P = 0.02$ )

**Conclusions:** The safety and efficacy profiles of esomeprazole plus rebamipide and omeprazole and rebamipide are similar for the treatment of ESD-induced ulcers. In large-sized ulcers, esomeprazole plus rebamipide promotes ulcer healing.

**Keywords:** endoscopic submucosal dissection, gastric neoplasm, esomeprazole, omeprazole, rebamipide

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*Japanese Clinical Medicine* 2013;4 7–13

doi: [10.4137/JCM.S11320](https://doi.org/10.4137/JCM.S11320)

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## Introduction

Currently, endoscopic submucosal dissection (ESD) is widely used as an alternative to surgical resection in patients with early-stage gastric cancer or adenoma.<sup>1</sup> Since ESD enables en bloc resection of large lesions, ESD results in the creation of larger artificial ulcers. Kakushima et al<sup>2,3</sup> have reported that gastric ulcers induced by ESD will heal within 8 weeks, regardless of size, location, *Helicobacter pylori* (*H. pylori*) infection, or the extent of gastric atrophy. Size reduction in the ulcers occurs by contraction in the early phase, and then regenerative mucosa covers the remaining mucosal defect within 8 weeks.<sup>4</sup> However, at 4 weeks, the ulcers of all cases remain in a healing stage.<sup>2</sup> Oh et al<sup>5</sup> reported that the initial ulcer size affects ulcer healing using proton pump inhibitors (PPI) at 4 weeks post-ESD. If the size of the post-ESD gastric ulcer is larger than predicted, PPI administration alone might not be sufficient for the ulcer to heal within 4 weeks.

Esomeprazole<sup>6</sup> is the S-isomer of omeprazole and was developed with the aim of improving the pharmacokinetic and pharmacodynamic profiles of racemic omeprazole. There is no report about the efficacy of post-ESD gastric ulcers by esomeprazole. On the other hand, rebamipide, which is a mucosal-protective antiulcer drug, promotes healing rates at 8 weeks for patients with ESD derived artificial ulcer.<sup>7</sup> Kato et al<sup>8</sup> showed that the combination of PPI plus rebamipide was more effective than the PPI alone for treating ulcers larger than 20 mm within 4 weeks of ESD. Woon Geon Shin et al<sup>9</sup> showed that PPI and rebamipide combination therapy had a superior 4-week ESD-induced ulcer healing rate and quality of ulcer healing compared with PPI monotherapy. Thus, PPI plus rebamipide combination therapy was generally effective for a 4-week ESD-induced ulcer healing rate, but in larger ESD-induced ulcers there were some issues that need to be addressed. Therefore, in the current study we assessed the efficacy of esomeprazole plus rebamipide combination therapy for ESD-induced ulcer healing compared with omeprazole plus rebamipide combination therapy.

## Patients and Methods

A total of 153 patients who underwent ESD for adenoma or early-stage gastric cancer at Saiseikai Wakayama Hospital from September 2007 to

August 2012 were included in this study. Of the 153 patients, 75 were excluded from analysis because they had been treated with other PPIs or had major organ failure. All procedures were performed after written informed consent was obtained from the patients. Patients receiving antiplatelet or anticoagulant agents were asked to stop these medications at least 4 days before study procedures took place. Accordingly, data from 29 esomeprazole and 49 omeprazole subjects were included for analysis. ESD was indicated in patients with adenoma accompanied by any degree of dysplasia and in patients with early superficial gastric cancer. We conducted a case-control study to compare healing rates within 4 weeks effected by esomeprazole plus rebamipide (group E) and omeprazole plus rebamipide (group O). The ESD technique has been precisely described elsewhere.<sup>1,10</sup> And All ESD was performed by a single endoscopist.

The knives used in ESD included FlusKnife, (DK2618JB, 1.5 mm type; Fujinon, Tokyo, Japan) and Insulation-tipped (IT) diathermic knife (KD-10 L; Olympus, Tokyo, Japan)<sup>1</sup> in this study. The ulcer created after resection was carefully examined, and any visible vessels were coagulated by hemostatic forceps (Radial Jaw™3 Hot Biopsy Forceps; Boston Scientific, Tokyo, Japan). The resected specimen was immediately pinned flat to a rubber plate to measure the size. The ulcer area was approximated from multiplication of the long diameter and the diameter perpendicular to the long diameter of the resected specimen. The sizes of the artificial ulcers were divided into normal size (area < 1,200 mm<sup>2</sup>) or large size (area ≥ 1,200 mm<sup>2</sup>).<sup>11</sup> Multifragment resection was considered incomplete, even when the lesion was completely removed endoscopically.

Post procedure-related bleeding was defined as that when hematemesis, melena, or hemoglobin concentration decreased by more than 2 g/dL were observed. All bleeding was controlled by endoscopic treatments such as hemoclipping, epinephrine injection, electrocoagulation, argon plasma coagulation (APC), and hemostatic forceps. Perforation was diagnosed endoscopically by direct observation of mesenteric fat just after resection or by the presence of free air on radiographs or the CT image.<sup>12</sup> After ESD, all patients received intravenous administration of 20 mg omeprazole (Omepral injection; Astra Zeneca Co, Osaka, Japan) daily for the first 2 days,



followed by 4 weeks of drug treatment. The group E was administered 20 mg oral esomeprazole (Nexium; Astra Zeneca Co, Osaka, Japan) and 300 mg oral rebamipide (Mucosta; Otsuka Pharmaceutical, Tokyo, Japan) daily, whereas the group O was treated daily with 20 mg oral omeprazole (Omepral; Astra Zeneca Co, Osaka, Japan) and 300 mg oral rebamipide. Esophagogastroduodenoscopy was performed on the operative day, postoperative day (POD) 1, POD 7 and POD 28 in order to record the healing rates of each artificial ulcer, as well as any immediate complications. Ulcer stages were assessed using a six-stage system as proposed by Sakita and Fukutomi (Table 1) at 28 days after the ESD.<sup>13</sup>

Statistical comparisons of the patients were performed using the  $\chi^2$  test for categorical data and Student's *t*-test for numerical data. Data are expressed as mean  $\pm$  SD. Differences in the categorical variables between two groups were examined with the  $\chi^2$  test. A two-tailed *P* value of less than 0.05 was considered statistically significant.

## Results

Data regarding the clinical and endoscopic features of the patients are outlined in Table 2. *H. pylori* status was evaluated by either serological testing or urea breath test. Procedure time was measured from marking to the end of tumor removal. There were no significant differences between the two groups with respect to ulcer size, location of ulcer, tissue size, histopathology (included histopathology of subgroup) and positive *H. pylori*, except for age, gender and procedure time. Complications included post-procedure related bleeding in one patient from group E on the second day after ESD. 39 percent and 27 percent of the patients had S1 stage disease after 4 weeks of group O and E and there were no significant differences between the two groups with respect to healing rate of

S1 stage. To evaluate the effect of rebamipide plus PPI in large-sized or normal-sized ulcers, we performed a subgroup analysis of healing rates between the two groups. In group O, the healing rate of S1 stage in the large-sized ulcer was significantly lower than that of the normal-sized ulcer. By contrast, there were no significant healing rate differences between large-sized ulcer and normal-sized ulcer for the S1 stage in group E. In large-sized ulcers, a significantly higher healing rate of S1 stage were observed in the group E compared to group O, although there were no significant differences in normal-sized ulcers (Table 3). During follow-up, no significant side effects were associated with the medication taken in either treatment group. There were no cases of delayed gastric perforation or bleeding after discharge.

## Discussion

Endoscopic mucosal resection (EMR) is widely applied for curative treatment of gastric neoplasms such as early gastric cancer or adenoma. Recently, EMR has been replaced by ESD, because it is difficult to achieve en bloc resection of specimens larger than 20 mm with EMR; piecemeal resection leads to local recurrence with reported rates of about 15%.<sup>14,15</sup> The development of ESD has enabled performance of en bloc resections of lesions, irrespective of their size or location. Additionally, better pathological evaluation is achieved using en bloc specimens.<sup>16</sup> However, there have been concerns regarding the technical difficulties of the procedure, the cost, the long operation time and the higher incidence of complications such as bleeding or perforation compared with conventional EMR. Because ulcer dimensions are larger and the resection depths are greater than those associated with EMR, the risk of bleeding is believed to be higher. Bleeding from the ulcer is the most serious complication during and after ESD.<sup>17</sup> Green et al<sup>18</sup> and Berstad<sup>19</sup> have shown that the intragastric pH should

**Table 1.** Gastric ulcer stages classified using a 6-stage system.

Stage	Endoscopic definition
A1 (active stage 1)	Ulcer that contains mucus coating, with marginal elevation because of edema
A2 (active stage 2)	Mucus-coated ulcer with discrete margin and less edema than active stage 1
H1 (healing stage 1)	Unhealed ulcer covered by less than 50% regenerating epithelium with or without converging folds
H2 (healing stage 2)	Ulcer with mucosal break but almost covered with regenerating epithelium
S1 (scar stage 1)	Red scar with rough epithelialization without mucosal break
S2 (scar stage 2)	White scar with complete re-epithelialization

**Table 2.** Baseline Characteristics of Patients.

	group O (n = 49)	group E (n = 29)	P-value
Age, mean (range), years	69.9 ± 9.3 (46–84)	76.1 ± 6.7 (63–86)	<i>P</i> = 0.0023
Sex (Female/Male)	38/11	16/13	<i>P</i> = 0.038
<i>H. pylori</i> (positive/negative/ND)	21/19/9	10/8/11	n.s.
Anti-platelet agents (Y/N)	8/41	7/22	n.s.
Alcohol (Y/N)	15/34	14/15	n.s.
Smoking (Y/N)	15/34	9/20	n.s.
Diabetes mellitus (Y/N)	13/36	8/21	n.s.
Lesion size, mean (range), mm	14.7 ± 11.3 (3–55)	13.8 ± 10.2 (3–53)	n.s.
Location (U/M/L)	9/23/17	1/16/12	n.s.
Macroscopic type			n.s.
protruded type (0-I, 0-II a)	25	16	
depressed type (0-II c)	24	13	
flat type (0-II b)	0	0	
Tumor depth			n.s.
Adenoma	20	7	
M	28	22	
SM1	1	0	
SM massive	0	0	
En bloc resection (Y/N)	46/3	28/1	n.s.
Resected size, mean (range), mm	36.9 ± 14.0 (15–75)	34.2 ± 14.3 (20–83)	n.s.
Procedure time, mean (range), min	64.2 ± 51.8 (15–260)	38.0 ± 29.6 (11–130)	<i>P</i> = 0.015
Post procedure-related bleeding	0/49	1/29	n.s.
Perforation	0/49	0/29	n.s.
Post-ESD ulcer healing stage at 1 week (H1/H2/S1)	49/0/0	29/0/0	n.s.
Post-ESD ulcer healing stage at 4 weeks (H1/H2/S1)	7/23/19	4/17/8	n.s.

**Note:** Continuous data are expressed as mean ± standard deviation and (minimum-maximum).

**Abbreviations:** ND, not detected; ns, not significant; L, lower third; M, middle third; U, upper third; SM1, minimally invasive carcinoma with infiltration depth ≤ 500µm.

be ≥6.0 in order to allow platelet aggregation and prevent platelet disaggregation. Therefore, inhibitors of gastric acid secretion such as PPIs and histamine-2-receptor antagonists (H2-RAs) have been administered after endoscopic therapy for gastric neoplasms to keep the pH of gastric juice high and to induce rapid ulcer healing.<sup>17,20–23</sup> Kakushima et al<sup>22</sup> have shown that after ESD, artificial ulcers treated by normal-dose PPI therapy healed within 8 weeks regardless of size and location. There is no consensus, however, regarding optimal treatment durations and drug regimens for relatively large ESD-induced ulcers. Kakushima et al<sup>3</sup> have also shown that 4 weeks of PPI treatment was not enough for a large post-ESD ulcer to heal, and that 8 weeks was required. Oh et al<sup>5</sup> had reported that the degree of healing of ESD-induced ulcers was dependent on the initial ulcer size, indicating that the duration of treatment with PPI should be considered. Taking these data into consideration, it seems that the administration of a PPI alone may not be sufficient for a large ESD-induced ulcer to heal within 4 weeks.

Bleeding, which always occurs within 2 weeks of ESD, is the most common complication with surgical-based artificial ulcers. The most effective strategy to prevent bleeding from an artificial ulcer after ESD is to promote quick recovery from mechanical and artificial gastric mucosal wounds. In most patients, short-term administration of a PPI or H2-RAs may be sufficient to heal artificial ulcers; however, in some patients the ulcer does not heal at an early stage, even after 8 weeks of PPI administration. This inability to heal may be due to severe atrophic gastritis, which commonly requires dissection of larger areas of mucosa. In addition, the more extensive dissection of the gastric submucosa, just above the muscularis propria, which is required for the assessment of cancer spread of lymphovascular invasion may also delay ulcer healing.<sup>7</sup> Although there have been several reports comparing PPIs and H2RAs for the prevention of delayed bleeding and the promotion of the healing of ESD-induced ulcers, the reported results conflict.<sup>21,24,25</sup> Some authors report that PPI therapy is superior to H2-RAs therapy<sup>21,24</sup> while others find no differences between the 2 therapies.<sup>25,26</sup> Furthermore,

**Table 3.** Subgroup analysis in accordance with ulcer size.

group O			P-value	group E			P-value
resected specimen area	large-sized	normal-sized		resected specimen area	large-sized	normal-sized	
H1	5	2	$P < 0.00001$	H1	3	1	$P = 0.07$
H2	13	10		H2	3	13	
S1	0	19		S1	2	7	
total	18	31		total	8	21	
healing rate of S-stage	large-sized	normal-sized		healing rate of S-stage	large-sized	normal-sized	
	0%(0/18)	61.2%(19/31)	$P < 0.00001$		25%(2/8)	33.3%(7/21)	$P = 0.66$
Large-sized ulcer			P-value	Normal-sized ulcer			P-value
resected specimen area	group O	group E		resected specimen area	group O	group E	
H1	5	3	$P = 0.09$	H1	2	1	$P = 0.10$
H2	13	3		H2	10	13	
S1	0	2		S1	19	7	
total	18	8		total	31	21	
healing rate of S-stage	large-sized	large-sized		healing rate of S-stage	normal-sized	normal-sized	
	0%(0/18)	25%(2/8)	$P = 0.02$		61.2%(19/31)	33.3%(7/21)	$P = 0.09$

**Abbreviations:** H1, Healing stage 1; Hh2, Healing stage 2; Ss1, Scarring stage 1.

several authors have reported that PPI and rebamipide combination therapy had a 4–8 week ESD-induced ulcer healing rate compared with PPI monotherapy.<sup>7,27</sup> Other authors have reported that rebamipide promotes ulcer healing in large-sized ESD-induced ulcers within 4–6 weeks after ESD.<sup>8,11</sup> These results could be explained by the regulatory action of rebamipide in the inflammatory processes. Rebamipide promotes the ulcer healing process by increasing the level of cytoprotective prostaglandin, epidermal growth factor, or nitric oxide, and decreasing the level of oxygen free radical. These actions of rebamipide could promote gastric mucosal blood flow at the ulcer margin, an important factor in ulcer healing, and accelerate mucosal or submucosal reconstruction of damaged structure.<sup>27</sup> Taking these data into consideration, it seems that the administration of a PPI alone may not be sufficient for a post ESD-induced ulcer to heal within 4 weeks.

In the present study, the number of ulcers that reached the scar stage was larger, but not significantly larger, in group E (27%) than in group O (39%) at 4 weeks after ESD. Kato et al<sup>8</sup> have reported that the combination of PPI plus rebamipide was significantly more effective than PPI alone for treating ulcers larger

than 20 mm at 4 weeks after ESD. The endpoint ulcers reached the scar stage in the PPI group (36%) and in the combination group (68%). There may have been a difference in the ulcer scarring rate because of possible differences in the baseline data such as the use of anti-platelet or inflammatory drugs. However, several authors have reported that artificial ulcers reached the scar stage at 4 weeks after EMR/ESD in 17% of the PPI group,<sup>28</sup> 15% of the PPI group,<sup>17</sup> and approximately 10% of the PPI group,<sup>5,29</sup> which were similar to our scarring rate results in both groups at 4 weeks. On the other hand, there is no report about the efficacy of post ESD induced ulcers by esomeprazole. Esomeprazole was developed as a single optical isomer of racemic omeprazole and, accordingly, has demonstrated some pharmacological advantages. In particular, a higher oral bioavailability is thought to contribute to the greater degree of acid suppression with esomeprazole than omeprazole, and differences in metabolism pathways are thought to contribute to less interpatient variability with esomeprazole.<sup>6</sup> Findings from studies in healthy volunteers, patients with gastro-esophageal reflux disease (GORD) or those with continuous





NSAID therapy have shown that, by day 5, once-daily oral esomeprazole at doses of 20 or 40 mg is more effective at increasing intragastric pH to >4 than once-daily lansoprazole, omeprazole, pantoprazole or rabeprazole. During day 5, the mean percentage of time that intragastric pH was >4 with daily esomeprazole 40 mg was significantly greater than that with comparator PPIs.<sup>6</sup> Therefore, we assessed the efficacy of esomeprazole plus rebamipide combination therapy for ESD-induced ulcer healing compared with omeprazole plus rebamipide combination therapy. In our results, there were no significant differences between the two groups with respect to healing rate of S1 stage at 4 weeks after ESD, but in subgroup analysis, regarding large-sized ulcers, a significantly higher healing rate of the S1 stage was observed in group E compared to group O. This result suggests that esomeprazole plus rebamipide combination therapy was found to be more effective than omeprazole plus rebamipide combination therapy for large ESD-induced artificial ulcers ( $\geq 1200$  cm<sup>2</sup>). Because rapid ulcer healing through clot stabilization at an elevated intragastric pH is required, a strong acid suppressant such as esomeprazole is more effective with respect to healing rate of S1 stage at 4 weeks after ESD.

Although a PPI is certain to be the most useful drug with healing effects for post ESD-induced ulcer, recent reports have confirmed a number of patients who are PPI-refractory (resulting from PPI metabolism, such as that occurring via CYP2C19).<sup>30</sup> Therefore, clinical research on therapeutic options other than acid-suppressing agents has been needed. There appears to be less variability in the pharmacokinetics of esomeprazole in the overall population compared with other PPIs, because esomeprazole appears to be less dependent on CYP2C19 genetics.<sup>6</sup> Thus, at this point, although CYP2C19 genotyping of the patients could not be performed in this study, esomeprazole may show a high degree of stability in the treatment of post ESD-induced ulcer.

This study has some limitations. First, this is a case-control study. Second, the sample size was relatively small. Large-scale, controlled studies are needed to verify the effectiveness of 4 weeks of esomeprazole plus rebamipide combination therapy in the prevention of late bleeding, as well as to investigate its effects on quality of ulcer healing. Third, the study

was performed in a single center by an experienced endoscopist.

## Conclusions

In conclusion, to the best of our knowledge, the present report is the first retrospective study to demonstrate that the safety and efficacy profiles of esomeprazole plus rebamipide and omeprazole plus rebamipide are similar for the treatment of ESD-induced ulcers. Especially in large-sized ulcers, esomeprazole plus rebamipide promotes ulcer healing.

## Funding

Author(s) disclose no funding sources.

## Author Contributions

Conceived and designed the experiments: MB. Analyzed the data: MB. Wrote the first draft of the manuscript: MB. Contributed to the writing of the manuscript: MB, KG, KY, MK. Agree with manuscript results and conclusions: MB, KG, KY, MK. Jointly developed the structure and arguments for the paper: MB, KG, KY, MK. Made critical revisions and approved final version: MB. All authors reviewed and approved of the final manuscript.

## Competing Interests

Author(s) disclose no potential conflicts of interest.

## Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest. Saiseikai Wakayama Hospital obtained ethical approval for the use of esomeprazole in the ESD

treatment of the patients whose records are reviewed in this research.

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