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【 ORIGINAL ARTICLE 】

Randomized Controlled Trial Comparing the Effects of Vonoprazan Plus Rebamipide and Esomeprazole Plus Rebamipide on Gastric Ulcer Healing Induced by Endoscopic Submucosal Dissection

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Abstract:

Objective Gastric endoscopic submucosal dissection (ESD) is currently a standard procedure, and proton pump inhibitors (PPIs) are most commonly used to treat post-ESD ulcers. Vonoprazan, a potassium-competitive acid blocker (P-CAB), reportedly inhibits gastric acid secretions more effectively than PPIs. Combination therapy of a PPI plus rebamipide is effective for treating larger ulcers. Our goal was to evaluate the effects of vonoprazan plus rebamipide compared to esomeprazole plus rebamipide for the treatment of post-ESD ulcers.

Methods First, vonoprazan plus rebamipide (V group) or esomeprazole plus rebamipide (E group) was orally administered to subjects for eight weeks. We then evaluated the ulcer healing process at four and eight weeks after the procedure using a gastric ulcer stage system and by measuring the ulcer size.

Patients A total of 84 patients who underwent ESD for gastric neoplasms between September 2015 and December 2017 in Tsuchiura Kyodo General Hospital were included in this randomized controlled trial.

Results The ulcer scar rates at week 4 in the V group (n=43) and E groups (n=39) were 20.9% and 15.4%, while those at week 8 were 90.7% and 92.3%, respectively. The ulcer reduction rates at week 4 in the V and E groups were 94.6% and 93.8%, and those at week 8 were 99.7% and 99.3%, respectively. The ulcer scar rates and reduction rates were not significantly different between the two groups.

Conclusion Combination therapy consisting of vonoprazan plus rebamipide was not superior to that of esomeprazole plus rebamipide for post-ESD ulcer healing (UMIN000019516).

Key words: endoscopic submucosal dissection, gastric intraepithelial neoplasm, artificial ulcer, ulcer healing, vonoprazan, esomeprazole

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Introduction

Endoscopic submucosal dissection (ESD) has recently become a standard procedure for treating gastric intraepithelial neoplasms (gastric adenoma and early gastric cancer) (1). While ESD more effectively allows for *en bloc* resection of large lesions than endoscopic mucosal resection (EMR), the artificial ulcers induced by the procedure are proportionately large. There have been some reports of artificial ulcers induced by ESD. Kakushima et al. (2, 3) reported that post-ESD gastric ulcers heal within eight weeks regardless of size, location, *Helicobacter pylori* infection status, and gastric atrophy extent. Artificial ulcers theoretically remaining in the submucosal layer are thought to heal faster than peptic ulcers.

Several studies have reported that proton pump inhibitors (PPIs) are effective at preventing postprocedural bleeding and induce prompt healing of artificial ulcers. PPIs are widely used to treat artificial ulcers. Oh et al. (4) reported that the initial ulcer size affects the ulcer healing achieved with PPIs at four weeks post-ESD. If the post-ESD ulcer is

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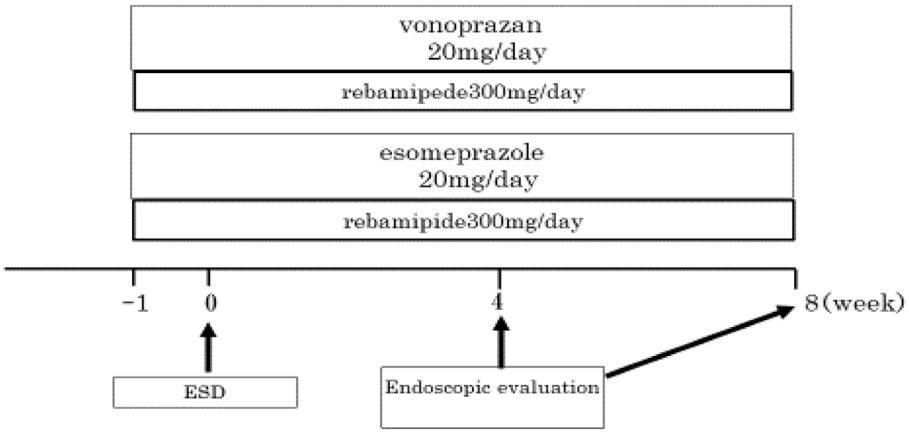

Figure 1. **Treatment protocol.**

larger than predicted, PPI administration alone may not be sufficient for treatment. Kato et al. (5) reported that the combination of a PPI and rebamipide was more effective than a PPI alone for treating ulcers >20 mm within 4 weeks post-ESD.

Esomeprazole, an *S*-isomer of omeprazole and a new PPI, reportedly showed stronger inhibition of gastric acid secretion than conventional PPIs (6). In a previous single-arm trial, we evaluated the effects of esomeprazole alone on the healing process of post-ESD gastric ulcers. In that study, ulcer scar rates (S1/S2 stage) at four and 8 weeks post-ESD were 28.6% [95% confidence interval (CI), 17.8-42.4%] and 98% (95% CI, 89.3-99.6%), respectively (7).

Vonoprazan, an orally active potassium competitive acid blocker (P-CAB), first received global approval for the treatment of acid-related diseases in Japan. This P-CAB inhibits gastric H^+ and K^+-adenosine triphosphatase and can reportedly inhibit gastric acid secretions more effectively than PPIs (8). However, few reports have described the artificial ulcer healing process induced by vonoprazan (9).

We hypothesized that combination therapy consisting of vonoprazan plus rebamipide would be the most effective treatment for ulcer healing. The aim of this study was to evaluate the effects of vonoprazan plus rebamipide compared to esomeprazole plus rebamipide regarding the healing of artificial ESD-induced ulcers.

Materials and Methods

Study design

This prospective randomized controlled study was performed at a single center. The protocol was approved by the Ethics Committee of Tsuchiura Kyodo General Hospital and registered with the University Hospital Medical Information Network (UMIN) as "A randomized controlled trial to compare the effects of vonoprazan and esomeprazole on gastric ulcer healing induced by endoscopic submucosal dissection" (UMIN000019516).

Patients

Patients who underwent ESD for gastric neoplasms at Tsuchiura Kyodo General Hospital were included in this prospective trial. Each patient provided their written informed consent prior to participating. We excluded from this trial patients who had an allergy to the trial drugs, were or might become pregnant, were lactating, or had severe liver or heart dysfunction.

Protocol

After study enrollment, patients were randomly assigned to either of 2 groups: those who received vonoprazan fumarate 20 mg plus rebamipide 300 mg (V group) and those who received esomeprazole 20 mg plus rebamipide 300 mg (E group). Both groups took the trial drugs orally for 8 weeks starting 7 days before the procedure (Fig. 1).

The *H. pylori* infection status was examined serologically. A viral load >10 IU/mL was defined as positive for an *H. pylori* infection. All patients received *H. pylori* infection eradication therapy after this trial. Upper gastrointestinal endoscopy was performed at four and eight weeks post-ESD. The ulcer was measured endoscopically and evaluated by gastric ulcer staging.

Randomization

A randomization number associated with a specific treatment was generated by the SAS program and then assigned to each subject.

Sample size

In our previous trial, the scar ratio (S1/S2) of artificial ulcers after treatment with esomeprazole alone was 28.6% at 4 weeks after the procedure. The scar stages of PPI alone and of PPI plus rebamipide at 4 weeks post-ESD were reportedly 36% and 68%, respectively (5). We hypothesized that vonoprazan would be as effective as a PPI used in combination with rebamipide for treating ESD-induced ulcers.

We assumed scar ratios at 4 weeks of 20% and 50% with the esomeprazole plus rebamipide and vonoprazan fumarate

Table 1. Gastric Ulcer Stages Classified Using a 6-stage System.

Stage	Endoscopic definition
A1 (active stage 1)	Ulcer that contains mucus coating, with maginal elevation because of edema
A2 (active stage 2)	Mucus-coated ulcer with discretemargin 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 1)	Ulcer with mucosal break but almost covered with regenerating epithelium
S1 (scar stage 1)	Red scar with rough epithelization without mucosal break
S2 (scar stage 2)	White scar with complete re-epithelization

plus rebamipide regimens, respectively. Assuming an alpha value of 0.05 and power of 0.80, the inclusion of >39 subjects in each group was deemed sufficient to identify a clinically relevant difference. Accordingly, the inclusion of >80 subjects was deemed sufficient for this trial.

Endpoints

The primary endpoint was the ulcer scar rates and the gastric ulcer reduction rate at four and eight weeks post-ESD. The secondary endpoint was the frequency of bleeding at four and eight weeks post-ESD. Upper gastrointestinal endoscopy was performed at four and eight weeks post-ESD. We evaluated ulcer scar rates using a gastric ulcer staging system (10) (Table 1) and measured the ulcer size. The initial ulcer size was defined as the specimen's length and width. The ulcer size was defined as the length×width (mm^2), while the ulcer reduction rate was defined as follows:

[initial ulcer size]-[ulcer size at 4 or 8 weeks post-ESD]/[initial ulcer size]×100(%)

Delayed bleeding was defined as clinically evident bleeding that required emergency endoscopy and/or a blood transfusion with a decline in the serum hemoglobin concentration of >2 g/dL.

ESD

The indications for ESD included intramucosal differentiated-type early gastric cancer (EGC) of any size without ulceration or signs of submucosal invasion, intramucosal differentiated-type EGC <30 mm in diameter with a scar but no lymph node involvement or distant metastases, and undifferentiated-type EGC <20 mm in diameter without a scar.

ESD was performed with a conventional singe-channel endoscope with a forward water-supply function (GIF-H260 Z or Q260J; Olympus, Tokyo, Japan). The ESD process is shown in Fig. 2. The Dual Knife (KD-650L; Olympus) was the most commonly used endoscopic device. Hyaluronic acid solution was injected into the submucosal layer for the mucosal incision, while physiological salt solution was used for submucosal dissection. The ESD-induced ulcer was carefully examined, and any visible vessels were coagulated by homeostatic forceps (FD-410 L; Olympus). A VIO300D electrosurgical generator (ERBE, Tuebingen, Germany) was used, and the ESD procedure was performed by two endoscopists. ESD was performed with the withdrawal of anticoagulant or antiplatelet therapy. All subjects underwent a scheduled second-look endoscopy. Anticoagulant or antiplatelet therapy was resumed after the second-look endoscopy.

Measurement of the ulcer size

We inserted a measuring device (M2-4K; Olympus) from the channel of the fiberscope until the scale touched the ulcer, whereupon a picture of the scale was taken to measure the ulcer length (maximum diameter) and width (crosswise maximum diameter) (Fig. 3). The ulcer measurements were decided after a conference between two endoscopists.

Statistical analyses

All statistical analyses were performed using the JMP version 10.0 software program (SAS Institute, Cary, USA). Data are expressed as the mean (range, minimum to maximum), and the level of significance was set at $p<0.05$. Fisher's exact test was used to compare the proportions of categorical variables (such as sex, comorbidities, *H. pylori* infection, tumor location, and scar rates), while the Mann-Whitney U-test was used to compare the medians of continuous variables (such as the age, ulcer size, and reduction rate).

Results

A total of 84 patients were enrolled in this study: 44 were randomly assigned to the V group, while the other 40 were randomly assigned to the E group. Two patients could not complete the study intervention since ESD was not completed due to bleeding (E group) or the lesion was unclear (V group). We therefore ultimately analyzed 43 patients in the V group and 39 in the E group (Fig. 4). The characteristics of the patients and lesions are summarized in Table 2; no significant intergroup differences were detected.

Ulcer scar rate [Sakita and Miwa classification (10)]

The ulcer grading scale is shown in Table 1. The ulcer scar rates 4 in the V and E groups at week were 20.9% (95% CI, 11.4-35.2%) and 15.4% (95% CI, 7.25-29.7%), while those at week 8 were 90.7% (95% CI, 78.4-96.3%) and 92.3% (95% CI, 79.7-97.3%), respectively. The scar rates were not significantly different between the two groups

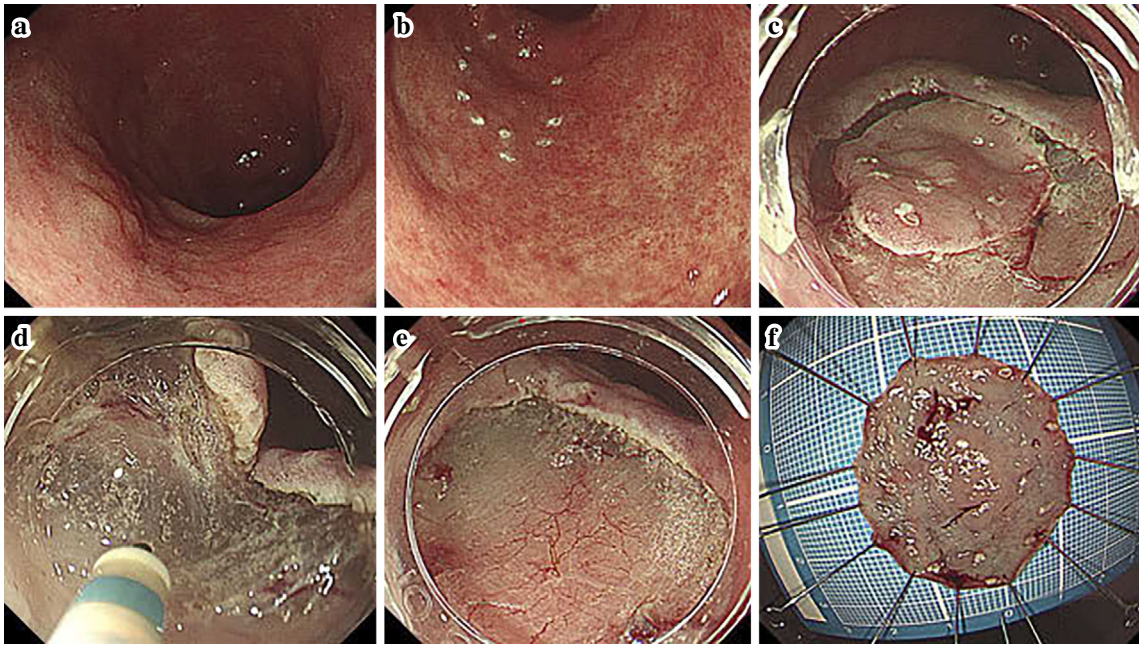

Figure 2. **Endoscopic submucosal dissection (ESD). The pictures of ESD process are shown. The lesion, an early gastric cancer, macroscopic type 0 IIa, 15mm in diameter, is located on the anterior wall in lower third (a). The markings are placed aroud the lesion (b). Hyaluronic acid solution was injected into the submucosal layer, then the mucosal layer is cut around markings (c). The submucosal layer is cut by the endoscopic knife (d). The ESD-induced ulcer was carefully examined, and any visible vessels were coagulated by homeostatic (e). The specimen is attached by pins, and measured the size (f).**

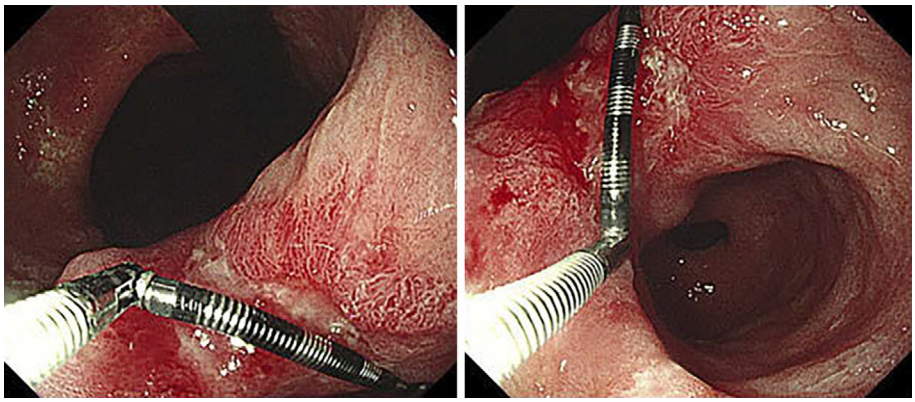

Figure 3. **Measurement of ulcer size.**

(Table 3).

Reduction rate

The ESD size, ulcer size, and ulcer reduction rates are shown in Table 3. The ulcer reduction rates in the V and E groups at week 4 were 94.6% (95% CI, 91.7-95.8%) and 93.8% (95% CI, 92.1-97.2%) and those at week 8 were 99.7% (95% CI, 99.2-100.2%) and 99.3% (95% CI, 98.2-100.2%), respectively. The reduction rates were not significantly different between the two groups (Fig. 5).

Complications

Delayed bleeding occurred in 1 patient in the V group (2.33%) and 4 patients in the E group (10.2%). In all patients, hemostasis was achieved endoscopically, but blood transfusions were required. No perforations occurred in either group. Mallory-Weiss syndrome occurred in one patient in the E group, while acute myocardial infarction occurred in one patient in the V group. The incidence of complications was not significantly different between the two groups (Table 4). No adverse events related to the study drugs were recorded.

Discussion

Endoscopic resection techniques, such as EMR and ESD,

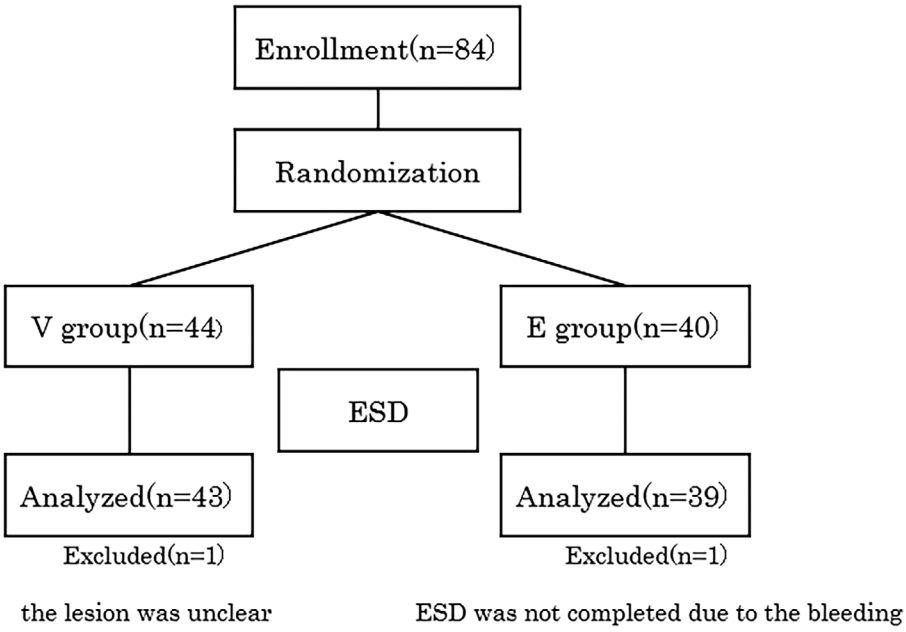

Figure 4. **Flow chart of study design and patient selection outcome.**

Table 2. **Characteristic of Patients**

	V group (43)	E group (39)	p value
Sex (Male/Female)	31/12	34/5	0.088
Age (years)	72.4 (52-89)	73.9 (58-88)	0.402
Comorbidities			
hypertensiton	20	21	0.501
diabetes mellitus	4	7	0.250
hemodialisis	1	0	0.254
liver cirrhosis	3	1	0.342
anticoagulant	4	3	0.794
antiplatelet drug	12	9	0.616
steroid	1	1	0.944
Helicobacter pylori infection	21	21	0.650
Macroscopic type			
protruded type (0-I, 0-IIa)	33	25	0.277
depressed type (0-IIc)	9	13	0.287
flat type (0-IIb)	1	1	0.944
Location (Upper/Middle/Lower)	7/12/24	4/18/17	0.248
Lesion (adenoma/cancer)	8/35	14/25	0.077
Tumor size (mm)	20.1 (7-40)	17.4 (6-42)	0.124
Size of resected specimen (mm)	39.9 (18-66)	38.6 (21-66)	0.656
En-bloc resection (%)	97.7	94.9	0.439
Opretating time (min)	97.2 (20-300)	95.4 (30-300)	0.511

are widely used in Japan. EMR is a fast and simple procedure, but it is difficult to achieve *en bloc* resection of lesions >20 mm in diameter. Piecemeal resection results in local recurrence in 15% of cases (11). ESD enables *en bloc* resection of larger lesions than EMR (1). The incidence of procedure-related complications, such as perforation and bleeding, is higher in cases treated by ESD than in those treated by EMR. Several countermeasures are reportedly effective for preventing complications. Delayed bleeding occurs in 0-5% of endoscopically treated patients (12, 13). To prevent delayed bleeding, post-ESD preventive coagulation is employed (14), and oral PPIs are thought to be more effective than histamine-2-receptor antagonists (H2-RAs) (15).

Artificial ulcers induced by ESD are typically larger than those induced by EMR. There are some reports describing the treatment of artificial ulcers. Bleeding from ulcers is considered among the most serious and challenging complications during and after ESD. Post-ESD bleeding usually occurs within two weeks of the procedure. Therefore, expediting the ulcer healing process is critical. Green et al. (16)

Table 3. Status of Artificial ESD-induced Ulcers at 4 and 8 Week after the Procedure.

	V group	E group	p value
Size of ESD (mm^2)	1,375.7 (252-3,060)	1,404.2 (399-3,432)	0.790
4 weeks			
Ulcer stage (healing/scar)	34/9	33/6	0.515
Scar ratio (%)	20.9	15.4	
Ulcer area (mm^2)	95.6 (0-1,152)	88.2 (0-576)	0.287
Reduction rate (%)	94.6 (51.0-100.0)	93.8 (76.6-100.0)	0.296
8 weeks			
Ulcer stage (healing/scar)	4/39	3/36	0.794
Scar ratio (%)	90.7	92.3	
Ulcer area (mm^2)	7.0 (0-256)	14.7 (0-324)	0.833
Reduction rate (%)	99.7 (89.1-100.0)	99.3 (85.2-100.0)	0.848

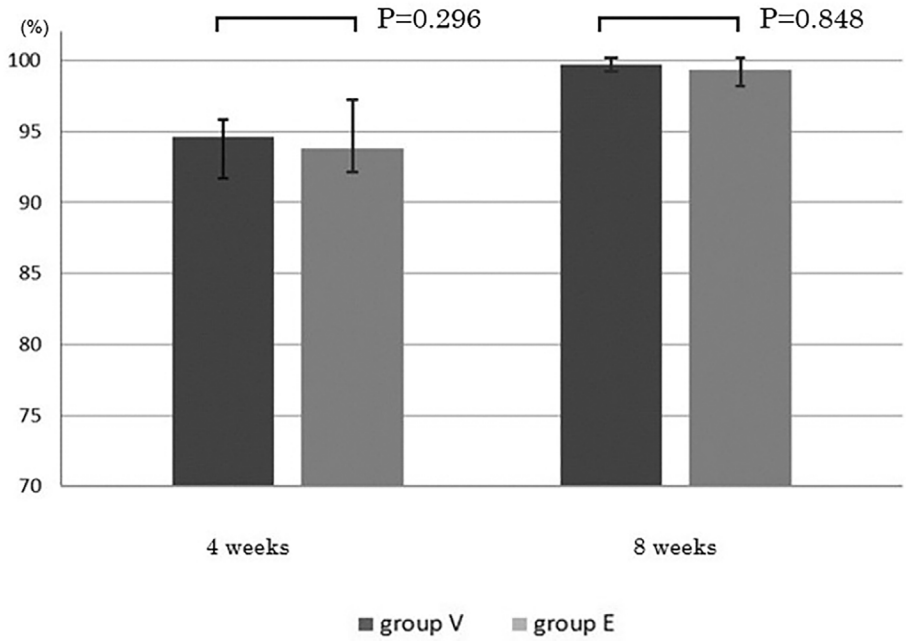

Figure 5. Reduction rates of gastric ulcers at 4 weeks and 8 weeks after the ESD. The ulcer reduction rates at week 4 in the V and E groups were 94.6% (95% confidence interval, 91.7-95.8%) and 93.8% (95% confidence interval, 92.1-97.2%) and those at week 8 were 99.7% (95% confidence interval, 99.2-100.2%) and 99.3% (95% confidence interval, 98.2-100.2%), respectively.

Table 4. Complications Related the Procedure.

	V group (43)	E group (39)	p value
Delayed bleeding	1 (2.33%)	4 (10.2%)	0.124
Perforation	0	0	
Mallory-Weiss syndrome	0	1	0.221
Acute myocardial infarction	1	0	0.254

suggested that the intragastric pH should be >6 to allow for platelet aggregation and prevent platelet disaggregation. Inhibitors of gastric acid secretion, such as PPIs and H2-Ras, are indispensable for ulcer healing and the prevention of post-ESD hemorrhaging. Uedo et al. (15) reported that PPI therapy is superior to H2-RA therapy for artificial ulcer healing. PPIs are more commonly used to treat post-ESD ulcers than other therapies.

Esomeprazole, which was developed as a single optical isomer of racemic omeprazole, has shown some pharmacological advantages. Its higher oral bioavailability than omeprazole contributes to its greater degree of acid suppres-

sion (6). The lower interpatient variability is likely related to the drug's unique metabolic pathway. Most PPIs are metabolized by CYP2C9 in the liver. Furuta et al. (17) reported on patients who were refractory to PPI treatment. The patients were grouped into rapid, intermediate, and poor metabolizers according to their CYP2C19 genotype. Esomeprazole appears to be less dependent on CYP2C19 than other PPIs; thus, it functions as a stronger gastric acid secretion inhibitor (6).

In our previous study, to evaluate the effectiveness of esomeprazole in healing ulcers, our patients were orally administered esomeprazole monotherapy. At week 4, ulcers reaching the scar stage were detected in 28.6% of cases (14/49), irrespective of the specimen size, with a delayed bleeding rate of 2.0% (1/49). This result may be related to the strong inhibitory potential of esomeprazole against gastric acid secretion as well as the use of a proper concentration of esomeprazole during the procedure by pre-administration of the agent for one week before endoscopic therapy. Andersson et al. reported that the area under the curve (AUC) of esomeprazole increased from day 1 to day 5, and there was a good correlation between the AUC and the effect of esomeprazole (18). Therefore, to achieve maximum acid suppression, the study agents, including esomeprazole, are administered for one week before the procedure. Bunno et al. (19) reported that esomeprazole plus rebamipide and omeprazole plus rebamipide had similar efficacies for treating ESD-induced ulcers but that the former was more effective in healing large ulcers.

Vonoprazan reportedly has pharmaceutical advantages over PPIs, including faster, stronger, and longer-lasting inhibition of gastric acid secretions. Sakurai et al. (8) reported that the acid-inhibitory effect of vonoprazan (pH>4 holding time ratio) was significantly greater than that of esomeprazole on days 1 and 7. Matsumoto et al. (20) reported that 7-day vonoprazan triple therapy was superior to 7-day PPI triple therapy as *H. pylori* eradication therapy. This result might have been due to the fact that vonoprazan differs from PPIs; it is able to achieve maximum suppression from the first day, whereas PPIs require three to five days to reach maximum acid suppression.

Tsuchiya et al. (9) reported no significant differences in the shrinkage rates of artificial ulcers between the vonoprazan group and the esomeprazole group until six weeks; however, at eight weeks, the vonoprazan group had a significantly superior shrinkage rate, reflecting the result of the cure rates. In that study, patients received intravenous omeprazole 20 mg for 2 days after the procedure. Thereafter, 2 days after ESD, vonoprazan or esomeprazole was administered orally. In our study, there were no significant differences in the scar rates of artificial ulcers between the V and E groups until eight weeks. This result may be related to the use of combination therapy.

Some factors are known to prolong ulcer healing, such as *H. pylori* infection, ulcer size, and ulcer location (21, 22). We evaluated the effect of these agents according to the stratification by age, sex, ulcer location, ulcer size, *H. pylori* infection. There were no significant differences in the scar stage at four weeks after the procedure (Table 5). This result may also be related to other factors, such as the presence of bile juice and delayed gastric emptying. The administration of vonoprazan reportedly increases the serum level of gastrin to a greater degree than the administration of PPIs (23), while the inhibition of gastric acid secretion and a high serum gastrin level correlate with delaying gastric emptying (24).

The benefits of combination therapy with mucosal protective antiulcer drugs, such as rebamipide or polaprezinc, and PPIs are controversial (25). Some authors have reported the beneficial effects of combination therapies. Rebamipide, a mucosal protective antiulcer drug, was effective at healing artificial ulcers. Kato et al. (5) reported that the combination of a PPI and rebamipide was more effective than the administration of PPI alone for healing ulcers >20 mm in diameter at week 4 after ESD. Polaprezinc, a cytoprotective agent, is also used to treat gastric ulcers. Inaba et al. (26) reported that, in patients treated with lansoprazole plus polaprezinc, ulcer healing was significantly faster and the incidence of protrusion of the ulcer base was significantly lower than in patients treated with lansoprazole alone. We hypothesized that combination therapy consisting of vonoprazan plus rebamipide would be the most effective for ulcer healing, but such effectiveness was not shown.

Delayed bleeding occurred less often in the V group than in the E group, but not to a significant degree. This result may be related to agent pre-administration and the use of combination therapy. If the sample size were larger, a significant difference might have be shown.

In patients pre-administered gastric acid secretion inhibitors, oral esomeprazole with a mucosal protective antiulcer drug may be sufficient to heal ulcers and prevent delayed bleeding.

Several limitations associated with the present study warrant mention. First, its sample size might not have been appropriate. We assumed a scar ratio at 4 weeks of 20% in the esomeprazole-treated group, which might have been underestimated, according to a previous report. Second, this trial was performed at a single center. Thus, additional studies are required to confirm our results.

Conclusion

Combination therapy consisting of vonoprazan plus rebamipide was not superior to combination therapy consisting of esomeprazole plus rebamipide for post-ESD ulcer healing and the prevention of delayed bleeding.

The authors state that they have no Conflict of Interest (COI).

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