

Combination of proton pump inhibitor and rebamipide, a free radical scavenger, promotes artificial ulcer healing after endoscopic submucosal dissection with dissection size >40 mm

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In our previous study, the healing effect of proton pump inhibitor plus rebamipide for endoscopic submucosal dissection-related artificial ulcer smaller than 40 mm showed statistical significance. However, such effect of the combination was not yet clear for ulcers with dissected diameter more than 40 mm. The aim of this present study was to resolve this problem under sufficient statistical power, with adequate sample size. We conducted a randomized controlled study. Either the proton pump inhibitor mono-therapy or the combination therapy was prescribed for 28 days after endoscopic submucosal dissection. Eighty-seven patients were eligible for outcome evaluation. Combination therapy was significantly superior to mono-therapy, 27.8% vs 0% reached healing stage (scar stage) in cases with ulcers of dissection diameter more than 40 mm. In conclusion, the combination therapy with rebamipide was favorable regimen in patients with larger artificial ulcer after endoscopic submucosal dissection.

Key Words: endoscopic submucosal dissection (ESD), proton pump inhibitor (PPI), rebamipide, artificial ulcer, ulcer healing

Endoscopic submucosal dissection (ESD) has become popular around the world to treat patients with early gastric cancer. The current interest in ESD is regarding its application for larger tumor size. As the problematic issue in ESD procedure, delayed bleeding after ESD from artificial ulcer was focused. Gotoda *et al.*⁽¹⁾ reported that frequency was up to 7%. Moreover, Uedo *et al.*⁽²⁾ demonstrated that the size of a tumor larger than 20 mm was an independent predictive factor for delayed bleeding. Okada *et al.*⁽³⁾ demonstrated that a dissected specimen of diameter greater than 40 mm was the only significant factor associated with delayed bleeding. Expand application of ESD lead to increase the risk of delayed bleeding from artificial ulcer. Moreover, bleeding in patients discharge is fatal. Therefore, management of larger size artificial ulcer is important. Although proton pump inhibitor (PPI) or H₂ receptor antagonist (H₂RA) is effective for the prevention of bleeding and the healing of artificial ulcer after ESD,^(2,4) it has a therapeutic limitation. In our previous study, the healing ratio in 4 weeks PPI mono-therapy was decreasing as larger as dissection specimen size: 33.3% (17/51) for specimen size <40 mm and 20.0% (2/10) for ≥40 mm.⁽⁵⁾ Administration of rebamipide, a cytoprotective agent, with PPI showed significantly superior

healing effect on ulcers with larger dissected size of 20 to 40 mm as compared with PPI mono-therapy. Such effect of the combination was suggested also for ulcers with a diameter greater than 40 mm: 75% (6/8) by the combination therapy and 20% (2/10) by the mono-therapy. However, there was no statistical significance ($p = 0.058$ by Fischer's exact test) because of less statistical power due to the small number of patients with such dissection size. Therefore, we conducted the following study to prove the healing effect of the combination therapy for artificial ulcer with a diameter greater than 40 mm with adequate sample size calculated from our previous data.

Methods

Subjects. This study was conducted from 2007 to 2010 at Gifu University Hospital Endoscopy Center and Gifu Municipal Hospital. The study protocol was approved by the Institutional Review Board for Human Research at each hospital. Inclusion criteria were all patients with gastric adenoma or early cancer who attended our hospitals for the purpose of ESD with a predicted resection size over 20 mm. Exclusion criteria were those with repeat bloody vomitus, major organ failure such as cardiac and pulmonary complications, or drug allergy. Those receiving concomitant administration of anticoagulants and anti-inflammatory drugs were also excluded. Written informed consent was obtained from all participants.

Study drugs and treatment schedule. Patients were admitted one day before ESD and hospitalized for at least 7 days post-ESD. All patients received an intravenous administration of omeprazole on the first two days after ESD. Participants then took either PPI (omeprazole 20 mg/day, lansoprazole 30 mg/day or rabeprazole 10 mg/day) alone or PPI plus 100 mg rebamipide 3 times/day for the following 26 days.

Endpoints. The primary endpoint was to evaluate the artificial ulcer healing ratio of the combination therapy compared with the PPI mono-therapy in all patients after ESD. The secondary endpoint was to evaluate the effect of the combination therapy in patients with a dissection size greater than 40 mm.

Outcome evaluation. Artificial ulcer healing was evaluated

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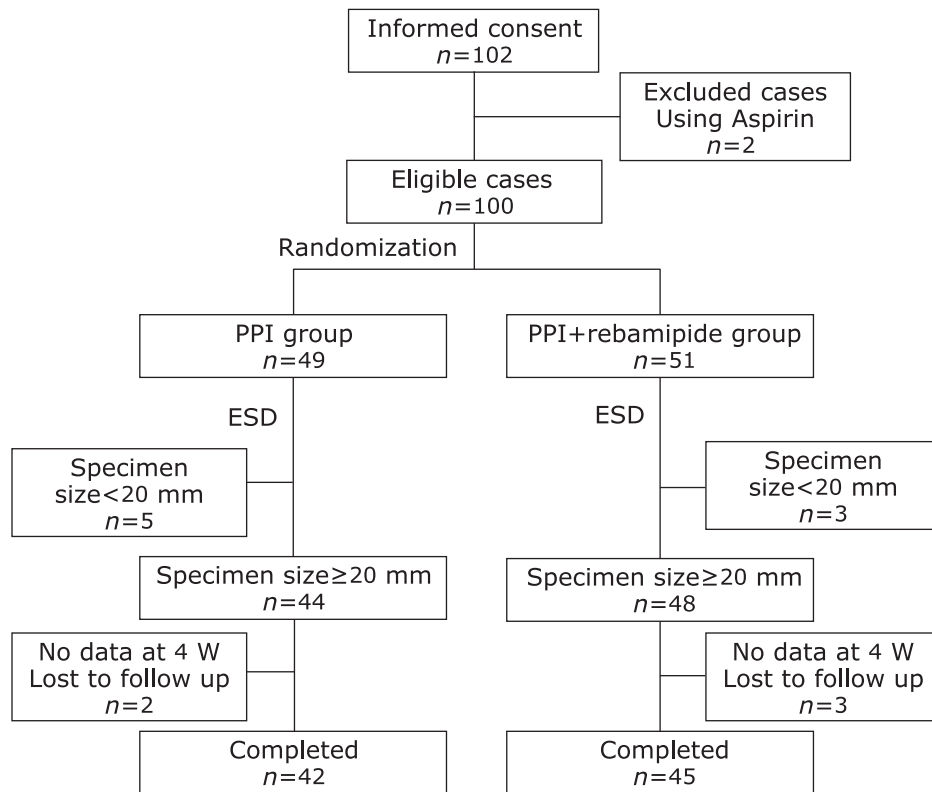


Fig. 1. Patient flow.

by endoscopy on the 28th day. The Sakita and Miwa classification, the scar stage was defined as healing of ulcer, was an evaluation scale for the ulcer stage.^(5,6) The dissection size was measured by pinning the specimen flat on a rubber plate. Endoscopic evaluation for the ulcer stage on the 28th day was judged by a representative blinded gastroenterologist, H.A. in Gifu University Hospital.

Calculation of the sample size. In our previous study on ESD ulcers ≥ 20 mm,⁽⁵⁾ 68% of patients in the combination group progressed to scar stage while only 35% progressed in the PPI mono-therapy group (33% improvement, $p = 0.011$). Therefore, at least a total of 35 cases were calculated as required sample size in one arm with α -error < 0.05 and β -error < 0.2 . Regarding cases with ulcer greater than 40 mm, 6 of 8 (75%) patients in the combination group progressed to scar stage as compared with 2 of 10 (20%) in the PPI mono-therapy group. These data indicate that at least 12 cases with such ulcer size were needed in one arm. In addition, only 30% of all patients had this artificial ulcer size in the previous study. Thus, the required number of total cases in one arm was 40. By adding 10% possible ineligibility in ulcer size and 10% dropouts, 48 was set as the target sample size in one arm.

Statistical analysis. Baseline demographic and clinicopathologic data were compared using the chi-square test or Mann-Whitney U test. We used the chi-square test or Fisher's exact test with a 95% confidence interval to compare the endpoint ulcer stage between the two groups. The significance of difference was declared with a p value of less than 0.05. All statistical analyses were performed using JMP ver. 8.0.2 software (SAS Institute, Cary, NC).

Results

Patient flow. As shown in Fig. 1, a total of 100 patients were eligible and randomly assigned to the two groups. ESD was

successfully performed and was judged as curative histopathologically in all cases. In 3 patients in the combination therapy group and in 5 cases in the PPI mono-therapy group, the dissected specimen size did not reach 20 mm. Lost to follow-up were 3 in the combination group, and 2 in the mono-therapy group.

Baseline demographic and clinicopathologic data. The baseline demographic and clinicopathologic data were not different between the 2 groups, as shown in Table 1.

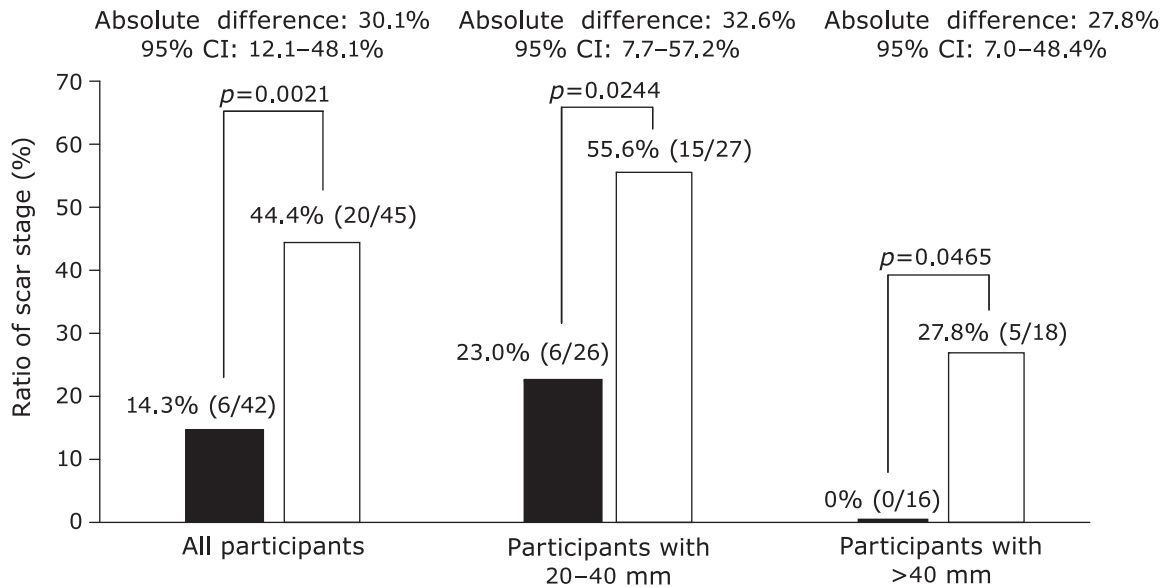
The effect of combination therapy. The ratio of S1 stage at 28 days after ESD was 6 of 42 (14.3%) in the mono-therapy group, and 20 of 45 (44.4%) in the combination group, respectively (absolute difference: 30.1, 95% CI: 12.1–48.1) ($p = 0.0021$) (Fig. 2). In cases with dissection diameter greater than 40 mm, the rate of S1 stage was 0 of 16 (0%) in the mono-therapy group, and 5 of 18 (27.8%) in the combination group (absolute difference: 27.8, 95% CI: 7.0–48.4) ($p = 0.0465$) (Fig. 2). For ulcers between 20 and 40 mm, the rates were 23.0% (6/26) and 55.6% (15/27), respectively (absolute difference: 32.6, 95% CI: 7.7–57.2) ($p = 0.0244$) (Fig. 2).

Discussion

In our previous data, the combination therapy was useful as compared with PPI mono-therapy for ESD-ulcer healing. However, the effect of the combination was not significant on ulcers larger than 40 mm,⁽⁵⁾ because the statistical power was insufficient due to the small sample size of this ulcer size. In order to address this concern, we analyzed the proportion of patients with larger ulcers in the total ESD cases referring to our previous data, and designed this study with 48 cases as the target for one arm. As a result, healing ratio of artificial ulcer rose in the combination therapy group by an absolute difference of 30.1% (95% CI: 12.1–48.1) in all cases. Moreover, the ratio was also improved by a similar

Table 1. Baseline demographic and clinicopathologic data of PPI alone and PPI + rebamipide combination groups

		PPI (n = 42)	PPI + rebamipide (n = 45)	
Age (years, median (range))		69.5 (52–85)	71 (45–87)	ns
Gender (male/female)		30/12	30/15	ns
Histopathology	Carcinoma	32	36] ns
	Adenoma	9	9	
	Cartinoid	1	0	
Localization of gastric tumor	Cardia	1	2] ns
	Body	20	17	
	Angle	8	11	
	Antrum	13	15	
Tumor size (mm, median (range))		18.5 (4–68)	18 (2–73)	ns
Specimen size (mm ² , median (range))		1130 (396–6059)	1024 (425–5740)	ns

**Fig. 2.** The ratio of Scar stage at 28 days after ESD. CI: confidential interval, chi-square test.

absolute difference of 27.8% (95% CI: 7.0–48.4) in ulcers larger than 40 mm.

Although PPI is the standard of care for ESD-related artificial ulcer and bleeding after ESD, Fujiwara *et al.*⁽⁷⁾ reported that PPIs and acid-suppressive agents alone have a limited effect in low acid secretion, such as severe atrophic condition in the gastric mucosa. Terano *et al.*⁽⁸⁾ reported that 7 weeks of rebamipide treatment without acid-suppressive agents promoted gastric ulcer healing after eradication therapy compared with a placebo treatment. Further evidence of the combination therapy for ESD ulcer has recently been added by Fujiwara *et al.*⁽⁷⁾

Rebamipide promote healing of mucosal injury by inducing the up-regulation of EGF and EGF receptors,⁽⁹⁾ and by phosphorylation of extracellular signal-regulated kinase (ERK) and activation of Rho kinase.⁽¹⁰⁾ Moreover, rebamipide maintained gastric mucosal integrity by increasing prostaglandin concentration.⁽¹¹⁾

Patients taking rebamipide concomitantly with PPI or H₂RA had mucosal injury less frequently than those taking acid suppressants plus other mucoprotective drugs.⁽¹²⁾ Our study design employed 4 weeks of treatment after ESD according to the report by Uedo *et al.*⁽²⁾ that most bleeding after ESD occurred within 28 days. Therapeutic strategy for artificial ulcer healing within 4 weeks may thus have a clinical significance to prevent bleeding after ESD. Major bleeding in both vomiting and stool was not actually observed in this study.

In conclusion, combination therapy for artificial ulcer healing within 4 weeks might be useful to prevent ESD-related complications in patients with larger dissection area.

Conflict of Interest

No potential conflicts of interest were disclosed.

References

- 1 Gotoda T. Endoscopic resection of early gastric cancer. *Gastric Cancer* 2007; **10**: 1–11.
- 2 Uedo N, Takeuchi Y, Yamada T, *et al.* Effect of a proton pump inhibitor or an H₂-receptor antagonist on prevention of bleeding from ulcer after endo-

- scopic submucosal dissection of early gastric cancer: a prospective randomized controlled trial. *Am J Gastroenterol* 2007; **102**: 1610–1616.
- 3 Okada K, Yamamoto Y, Kasuga A, *et al*. Risk factors for delayed bleeding after endoscopic submucosal dissection for gastric neoplasm. *Surg Endosc* 2011; **25**: 98–107.
 - 4 Takeuchi N, Umegaki E, Takeuchi T, Murano M, Yoda Y, Tokioka S, Higuchi K. Gastric ulcer healing after treatment of endoscopic submucosal dissection in Japanese: comparison of H₂ receptor antagonist and proton pump inhibitor administration. *J Clin Biochem Nutr* 2011; **49**: 216–221.
 - 5 Kato T, Araki H, Onogi F, *et al*. Clinical trial: rebamipide promotes gastric ulcer healing by proton pump inhibitor after endoscopic submucosal dissection—a randomized controlled study. *J Gastroenterol* 2010; **45**: 285–290.
 - 6 Sakita T, Fukushima H. Endoscopic diagnosis. In: Yoshitoshi Y, ed. *Ulcer of the Stomach and Duodenum* (in Japanese). Tokyo: Nankodo, 1971; 198–208.
 - 7 Fujiwara S, Morita Y, Toyonaga T, *et al*. A randomized controlled trial of rebamipide plus rabeprazole for the healing of artificial ulcers after endoscopic submucosal dissection. *J Gastroenterol* 2011; **46**: 595–602.
 - 8 Terano A, Arakawa T, Sugiyama T, *et al*. Rebamipide, a gastro-protective and anti-inflammatory drug, promotes gastric ulcer healing following eradication therapy for *Helicobacter pylori* in Japanese population: a randomized, double-blind, placebo-controlled trial. *J Gastroenterol* 2007; **42**: 690–693.
 - 9 Tarnawski AS, Chai J, Pai R, Chiou SK. Rebamipide activates genes encoding angiogenic growth factors and Cox2 and stimulates angiogenesis: a key to its ulcer healing action? *Dig Dis Sci* 2004; **49**: 202–209.
 - 10 Takagi T, Naito Y, Uchiyama K, *et al*. Rebamipide promotes healing of colonic ulceration through enhanced epithelial restitution. *World J Gastroenterol* 2011; **17**: 3802–3809.
 - 11 Tanigawa T, Watanabe T, Ohkawa F, *et al*. Rebamipide, a mucoprotective drug, inhibits NSAIDs-induced gastric mucosal injury: possible involvement of the downregulation of 15-hydroxyprostaglandin dehydrogenase. *J Clin Biochem Nutr* 2011; **48**: 149–153.
 - 12 Yamamoto T, Isono A, Mishina Y, *et al*. Gastroduodenal mucosal injury in patients taking low-dose aspirin and the role of gastric mucoprotective drugs: possible effect of rebamipide. *J Clin Biochem Nutr* 2010; **47**: 27–31.