J Rural Med 2016; **11**(2): 41–45

Original article

Effects of esomeprazole on the healing process of post-endoscopic submucosal dissection gastric ulcers: a single arm, prospective trial

Takashi Ichida[1], Fumihiko Kusano[1] and Yoshinori Sakai[1]

[1] *Department of Gastroenterology, Tsuchiura Kyodo General Hospital, Japan*

Abstract

Objectives: Gastric endoscopic submucosal dissection (ESD) is currently a standard procedure. ESD enables *en-bloc* resection of large lesions, while inducing larger artificial ulcers to a greater extent than conventional procedures. Several studies have reported that proton pump inhibitors (PPIs) prevent delayed bleeding and expedite the artificial ulcer healing process. Esomeprazole, an *S*-isomer of omeprazole, is reportedly one of strongest inhibitors of gastric acid secretion. Previous studies have examined the effectiveness of esomeprazole. Our goal was to verify the effects of esomeprazole on artificial ulcers in a prospective study. Methods: A total of 185 patients underwent ESD for gastric neoplasms at our hospital between January 2013 and June 2015. Among these 185 patients, 49 post-ESD scar lesions were included in this prospective trial. First, 20 mg esomeprazole was orally administered to all subjects before and after the procedure. We then evaluated the delayed bleeding rate and ulcer scarring rates at 4 weeks and 8 weeks after the procedure by using a gastric ulcer stage system. Results: There was one case of delayed bleeding (2.0%). Regardless of *Helicobacter pylori* infection status, ulcer scarring rates at weeks 4 and 8 were respectively 28.6% (14/49) and 98% (48/49). Conclusions: Our results suggest that oral administration of esomeprazole alone may be sufficient for prompt healing of artificial gastric ulcers induced by ESD (UMIN000009367).

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

(J Rural Med 2016; 11(2): 41–45)

Received: March 28, 2016
Accepted: June 27, 2016
Correspondence: Takashi Ichida, Department of Gastroenterology, Tsuchiura Kyodo General Hospital, 4-1-1 Otsuno, Tsuchiura, Ibaraki 300-0028, Japan
E-mail: taka_taka_0621@yahoo.co.jp

Introduction

Recently, endoscopic submucosal dissection (ESD) has become a standard procedure for treating gastric intraepithelial neoplasms (gastric adenoma and early gastric cancer)[1]. While ESD allows for *en-bloc* resection of large lesions compared with endoscopic mucosal resection (EMR), the sizes of 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 8 weeks, regardless of size, location, status of *Helicobacter pylori* infection, and extent of gastric atrophy. Artificial ulcers theoretically remaining in the submucosal layer are thought to heal faster than peptic ulcers.

Several studies reported that proton pump inhibitors (PPIs) are effective in preventing bleeding after the procedure and 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 status by PPI at week 4 of ESD. If the size of the post-ESD ulcer is larger than predicted, PPI administration alone may not be sufficient for treating ulcers. Kato *et al*.[5] reported that a combination of PPI and rebamipide was more effective than PPI alone for treating ulcers larger than 20 mm within 4 weeks of ESD.

Esomeprazole, an *S*-isomer of omeprazole, is a new form of PPI and was reported to show stronger inhibition of gastric acid secretion than conventional PPIs[6]. There are a few reports of the artificial ulcer healing process by esomeprazole. The aim of this study was to evaluate the efficacy of esomeprazole alone for artificial ulcers induced by ESD.

Methods

A total of 185 patients underwent ESD for gastric neoplasms at Tsuchiura Kyodo General Hospital between Janu-

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 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 2)	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

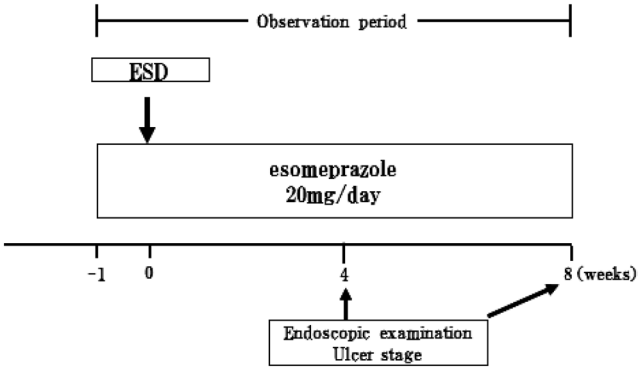


Figure 1 Study design. More than one week before the procedure, all patient were orally administered 20 mg/day esomeprazole; the drug was also administered at 8 weeks after the procedure.

ary 2013 and June 2015. Among the 185 patients, 49 post-ESD scar lesions were included in this prospective trial. Written informed consent was obtained for entry into the trial. An oral dose of esomeprazole (20 mg) was administered to all subjects. All subjects took esomeprazole once per day for 8 weeks. The primary endpoints were the ratio of delayed bleeding and ulcer scarring rates at 4 and 8 weeks after the procedure (Figure 1). Delayed bleeding was defined as clinically evident bleeding that required emergency endoscopic hemostasis and/or blood transfusion with a decline of more than 2 g/dL of hemoglobin. We evaluated ulcer scarring rates using a gastric ulcer staging system[7] (Table 1) at weeks 4 and 8 after the procedure.

The protocol was approved by the Ethics Committee of Tsuchiura Kyodo General Hospital.

ESDs were performed using a conventional singe-channel endoscope with forward water-supply function (GIF-H260Z or Q260J, Olympus, Tokyo, Japan). The endoscopy device in use was mainly the Dual Knife (KD-650L, Olympus). Hyaluronic acid solution was injected into the submucosal layer for mucosal incision and physiological salt solution was used for submucosal dissection. The ulcer induced by ESD was carefully examined, and any visible vessels were coagulated with hemostatic forceps (FD-410L, Olympus). VIO300D (ERBE, Germany) was used as an electrosurgical generator. An entire ESD process was performed by a single endoscopist.

All statistical analyses were performed using JMP version 10.0 software (SAS Institute, Cary, NC, USA). All data were expressed as the mean (range, minimum–maximum) and the level of significance was set at $P < 0.05$.

Results

Data regarding the clinical and endoscopic features of the patients are shown in Table 2. *H. pylori* infection status was evaluated by serological testing, and some patients received *H. pylori* eradication therapy in this study. The mean operating time was 76.7 (range, 15–180) min. The mean tumor size was 16.6 (range, 4–42) mm, and the mean size of resected specimens was 33.6 (range, 10–58) mm in diameter. *En-bloc* resection was attained in 93.4 (46/49)% of cases. No complications including perforation occurred during the trial except for one case of delayed bleeding.

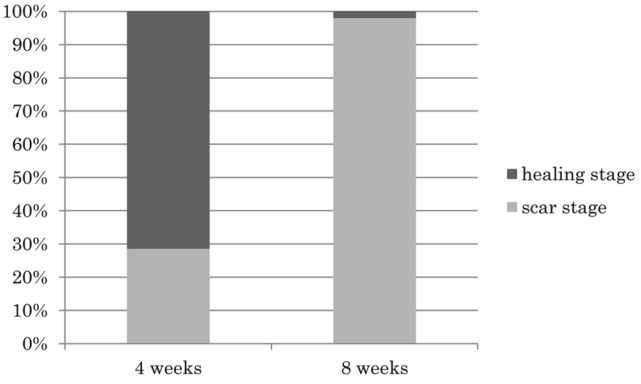
There was one case of delayed bleeding and the ratio was 2.0% (95% confidence interval (CI): 2.1–6.1%). We defined ulcer scarring as S1/S2 stage and ulcer scarring rates at 4 and 8 weeks were 28.6% (95%CI: 17.8–42.4%) and 98% (95%CI: 89.3–99.6%), respectively (Figure 2). We assessed each background factor to identify correlations with ulcer scarring at week 4 after the procedure by multiplex logistic analysis, but no significant factors were identified (Table 3).

Discussion

In Japan, gastric cancer is one of the most common cancers and was the second leading cause of cancer-related death among men and the third leading cause among women in 2013. The incidence of early gastric cancer is higher in Japan than in other countries[8]. Endoscopic resection techniques such as EMR and ESD are widely used in Japan. EMR is a fast and simple procedure, but it is difficult to achieve *en-block* resection of lesions larger than 20 mm in diameter. Piecemeal resection results in local recurrence

Table 2 Characteristics of patients

Sex (Male/Female)	39/10
Age (years)	Mean 73.3 (range, 58−87)
Comorbidities	
Hypertension	28
Diabetes mellitus	5
Liver cirrhosis	2
Hemodialysis	2
Anticoagulant	4
Antiplatelet drug	13
H. pylori. infection (yes/no/unknown)	20/22/7
Macroscopic type	
Protruded type (0-I, 0-II)	28
Depressed type (0-IIc)	20
Flat type (0-IIb)	1
Location (Upper/Middle/Lower)	6/17/26
Lesion (adenoma/cancer)	11/38
Tumor size (mm)	16.6 (range 4−42)
Size of resected specimen (mm)	33.6 (range, 10−58)
En-bloc resection	46 (93.4%)
Operating time (min)	76.7 (range, 15−180)



	4 weeks	8 weeks
H1 stage	7	0
H2	28	1
S1	14	47
S2	0	1

Figure 2 Ulcer stage at weeks 4 and 8 after ESD. Ulcer scarring rates (S1/S2) at weeks 4 and 8 of ESD were 28.6% (95%CI: 17.8–42.4%) and 98% (95%CI: 89.3–99.6%), respectively.

Table 3 Factors involved in ulcer scarring at week 4

	Odds ratio	P-value	95% confidence interval
Age	1.02	0.99	0.89–1.18
Location	0.98	0.98	0.12–8.67
Size of resected specimen	0.02	0.88	0.89–0.13
Operating time	1.00	0.54	0.98–1.05
Hypertension	0.23	0.19	0.02–1.96
Diabetes mellitus	7760	0.99	–
Liver cirrhosis	1552	0.99	–
Hemodialysis	0.73	1.00	–
Anticoagulant	0.00	0.99	0.00–32.8
Antiplatelet drug	0.47	0.75	0.02–5.87
H. pylori. infection	0.16	0.10	0.01–1.22

Multiplex logistic analysis. No significant factor was identified.

in 15% of cases[9]. 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 cases treated by EMR. Several countermeasures have been reported to be effective for preventing complications. Delayed bleedings occur in 0–5% of endoscopically treated patients[10, 11]. To prevent delayed bleeding, post-ESD preventive coagulation is effective[12] and oral intake of PPI, compared with histamine-2-receptor antagonist (H2-RA), is thought to be highly effective[13].

Artificial ulcers induced by ESD are typically larger than those by EMR. There are some reports describing the treatment of artificial ulcers. Bleeding from ulcers is considered to be one of the most serious and challenging complications during and after ESD. Post-ESD bleeding usually occurs within 2 weeks of the procedure. Therefore, expediting the process of ulcer healing is critical. Green *et al*.[14] suggested that intragastric pH should be greater than six in order to allow for platelet aggregation and prevent platelet disaggregation. Inhibitors of gastric acid secretion such as PPI and H2-RA are indispensable for ulcer healing and prevention of post-ESD hemorrhage. Uedo *et al*.[13] reported that PPI therapy is superior to H2-RA therapy for artificial ulcer healing. However, other studies reported no differences be-

tween the two therapies[15, 16]. PPIs are more commonly used for treating post-ESD ulcers than other therapies.

Furthermore, some authors reported the beneficial effects of combination of PPIs and anti-ulcer agents. Rebamipide, a mucosal protective antiulcer drug, was effective in the healing process of artificial ulcers. Kato *et al*.[5] reported that a combination of PPI and rebamipide was more effective than PPI alone for ulcers larger than 20 mm in diameter at week 4 of ESD. Polaprezinc, a cytoprotective agent, is also used for gastric ulcer treatment. Inaba *et al*.[17] 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 the patients treated with lansoprazole alone. To evaluate the effectiveness of esomeprazole in ulcer healing, our patients were administered mono-therapy with esomeprazole.

Previous studies have examined PPI administration. Kakushima *et al*.[3] reported that 4 weeks of PPI was not sufficient for healing of large post-ESD ulcers and concluded that 8 weeks of treatment were required. Arai *et al*.[18] reported that 2 weeks of PPI administration may be sufficient for ulcer healing. However, there is no consensus regarding the proper duration of PPI administration after ESD.

Esomeprazole was developed as a single optical isomer of racemic omeprazole and has shown some pharmacological advantages. A higher oral bioavailability contributes to a greater degree of acid suppression compared with omeprazole[6]. The lower interpatient variability is likely related to the unique metabolic pathway of the drug. Most PPIs are metabolized by CYP2C9 in the liver. Furuta *et al*.[19] reported a number of patients who were refractory to PPIs. Depending on the CYP2C19 genotypes, patients are grouped into three types: rapid metabolizer, intermediate metabolizer, and poor metabolizer. Esomeprazole appears to be less dependent on CYP2C19, and thus functions as a stronger gastric acid secretion inhibitor[6].

There have been a few reports of the impact of esomeprazole on the healing of artificial ulcers. Buuno *et al*.[20] reported that S1 stage was achieved at week 4 of ESD in 27.6%, and 38.7% of patients treated with esomeprazole plus rebamipide and omeprazole plus rebamipide, respectively. Arai *et al*.[18] compared the staging of post-ESD ulcers at week in patients receiving esomeprazole plus rebamipide for 2 weeks and 4 weeks, and found that the number of patients with ulcers in the healing/scar stage was 20/6 and 28/5, respectively. In these studies, patients received intravenous administration of 20 mg omeprazole for one or two days after the procedure. Wilder-Smith *et al*.[21] reported no significant differences between patients receiving intravenous and those receiving oral administration of esomeprazole with respect to amount of time for which mean intragastric pH was greater than 4 on day 1 or day 5 of treatment following administration with 20 or 40 mg. Therefore, our results suggest that esomeprazole should be administered more than one week before endoscopic therapy.

Kakushima *et al*.[2] reported that gastric ulcers induced by ESD heal within 8 weeks, but remain in the healing stage for 4 weeks. In this trial, at week 4, ulcers reaching the scarring stage were detected in 28.6% of cases irrespective of specimen size, with a delayed bleeding rate of 2.0%. This result may be related to the strong inhibitory potential of esomeprazole against gastric acid secretion, and the use of a proper concentration of esomeprazole during the procedure by pre-administering the agents for one week before endoscopic therapy.

Thus, oral esomeprazole administration alone may be sufficient for preventing delayed bleeding and for ulcer healing.

This trial has some limitations. First, this is a single arm study. Second, the sample size was small. Third, this study was performed in a single center. Additional studies are required to confirm our results.

Conclusion

Our results suggest that single-agent therapy with esomeprazole can be used as a standard therapeutic approach for treating artificial gastric ulcers induced by ESD. Single medication may contribute to better patient adherence. Omission of intravenous administration of PPI may also reduce the burden of doctors, nurses, and pharmacists during patient admission.

References

1. Ono H, Kondo H, Gotoda T, *et al*. Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001; 48: 225–229. [Medline] [CrossRef]
2. Kakushima N, Yahagi N, Fujishiro M, *et al*. The healing process of gastric artificial ulcers after endoscopic submucosal dissection. Dig Endosc 2004; 16: 327–331. [CrossRef]
3. Kakushima N, Fujishiro M, Yahagi N, *et al*. *Helicobacter pylori* status and the extent of gastric atrophy do not affect ulcer healing after endoscopic submucosal dissection. J Gastroenterol Hepatol 2006; 21: 1586–1589. [Medline] [CrossRef]
4. Oh TH, Jung HY, Choi KD, *et al*. Degree of healing and healing-associated factors of endoscopic submucosal dissection-induced ulcers after pantoprazole therapy for 4 weeks. Dig Dis Sci 2009; 54: 1494–1499. [Medline] [CrossRef]
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. [Medline] [CrossRef]

6. McKeage K, Blick SK, Croxtall JD, *et al*. Esomeprazole: a review of its use in the management of gastric acid-related diseases in adults. Drugs 2008; 68: 1571–1607. [Medline] [CrossRef]
7. Sakita T, Fukutomi H. Endoscopic diagnosis. In: Ulcer of the Stomach and Duodenum. Yoshitoshi Y, Ed. Nankodo, Tokyo, 1971: 198–208 (in Japanese).
8. Isomoto H, Yamaguchi N. Endoscopic submucosal dissection in the era of proton pump inhibitors. J Clin Biochem Nutr 2009; 44: 205–211. [Medline] [CrossRef]
9. Muto M, Miyamoto S, Hosokawa A, *et al*. Endoscopic mucosal resection in the stomach using the insulated-tip needle-knife. Endoscopy 2005; 37: 178–182. [Medline] [CrossRef]
10. Hotta K, Oyama T, Akamatsu T, *et al*. A comparison of outcomes of endoscopic submucosal dissection (ESD) For early gastric neoplasms between high-volume and low-volume centers: multi-center retrospective questionnaire study conducted by the Nagano ESD Study Group. Intern Med 2010; 49: 253–259. [Medline] [CrossRef]
11. Toyokawa T, Inaba T, Omote S, *et al*. Risk factors for perforation and delayed bleeding associated with endoscopic submucosal dissection for early gastric neoplasms: analysis of 1123 lesions. J Gastroenterol Hepatol 2012; 27: 907–912. [Medline] [CrossRef]
12. Takizawa K, Oda I, Gotoda T, *et al*. Routine coagulation of visible vessels may prevent delayed bleeding after endoscopic submucosal dissection—an analysis of risk factors. Endoscopy 2008; 40: 179–183. [Medline] [CrossRef]
13. 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 endoscopic submucosal dissection of early gastric cancer: a prospective randomized controlled trial. Am J Gastroenterol 2007; 102: 1610–1616. [Medline] [CrossRef]
14. Green FW Jr, Kaplan MM, Curtis LE, *et al*. Effect of acid and pepsin on blood coagulation and platelet aggregation. A possible contributor prolonged gastroduodenal mucosal hemorrhage. Gastroenterology 1978; 74: 38–43. [Medline]
15. Imaeda H, Hosoe N, Suzuki H, *et al*. Effect of lansoprazole versus roxatidine on prevention of bleeding and promotion of ulcer healing after endoscopic submucosal dissection for superficial gastric neoplasia. J Gastroenterol 2011; 46: 1267–1272. [Medline] [CrossRef]
16. Tomita T, Kim Y, Yamasaki T, *et al*. Prospective randomized controlled trial to compare the effects of omeprazole and famotidine in preventing delayed bleeding and promoting ulcer healing after endoscopic submucosal dissection. J Gastroenterol Hepatol 2012; 27: 1441–1446. [Medline] [CrossRef]
17. Inaba T, Ishikawa S, Toyokawa T, *et al*. Basal protrusion of ulcers induced by endoscopic submucosal dissection (ESD) during treatment with proton pump inhibitors, and the suppressive effects of polaprezinc. Hepatogastroenterology 2010; 57: 678–684. [Medline]
18. Arai M, Matsumura T, Okimoto K, *et al*. Two-week treatment with proton pump inhibitor is sufficient for healing post endoscopic submucosal dissection ulcers. World J Gastroenterol 2014; 20: 16318–16322. [Medline] [CrossRef]
19. Furuta T, Sugimoto M, Kodaira C, *et al*. CYP2C19 genotype is associated with symptomatic recurrence of GERD during maintenance therapy with low-dose lansoprazole. Eur J Clin Pharmacol 2009; 65: 693–698. [Medline] [CrossRef]
20. Bunno M, Gouda K, Yamahara K, *et al*. A cas- control study of esomeprazole plus rebamipide vs. omeprazole plus rebamipide on post-ESD gastric ulcers. Jpn Clin Med 2013; 4: 7–13. [Medline] [CrossRef]
21. Wilder-Smith CH, Bondarov P, Lundgren M, *et al*. Intravenous esomeprazole (40 mg and 20 mg) inhibits gastric acid secretion as effectively as oral esomeprazole: results of two randomized clinical studies. Eur J Gastroenterol Hepatol 2005; 17: 191–197. [Medline] [CrossRef]