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RANDOMIZED CONTROLLED TRIAL

Two-week treatment with proton pump inhibitor is sufficient for healing post endoscopic submucosal dissection ulcers

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Abstract

AIM: To investigate the optimum period of treatment for post endoscopic submucosal dissection (ESD) ulcers.

METHODS: Patients who underwent ESD for gastric cancer were randomized to two groups and treated with esomeprazole 20 mg per day for 4 wk (4W group) or 2 wk (2W group). At 4 wk after ESD, we measured the size of the artificial ulcers by endoscopy and determined the ulcer healing rate, compared with the size of the ESD specimens. This randomized controlled trial study was approved by our ethics committee and registered in the UMIN Clinical Trial Registry.

RESULTS: A total of 60 consecutive patients were included in the study. All patients received rebamipide 300 mg per day for 4 wk. One patient in 2W group who showed bleeding within two weeks and received endoscopic treatment was excluded from further analysis. The numbers of patients with ulcers in the healing/scar stage in the 2W and 4W groups at 4 wk after ESD were 20/6 and 28/5, respectively, with no significant difference. The ulcer healing rate in the 2W and 4W groups were 96.1% [95% confidence interval (CI): 94.6%-97.55] *vs* 94.8% (95%CI: 92.6%-97.1%), respectively, with no statistical difference (UMIN000006951).

CONCLUSION: Two-wk treatment with a proton pump inhibitor is as effective as four-week treatment for healing post ESD ulcers.

Key words: Proton pump inhibitor; Endoscopic submucosal dissection; Esomeprazole; Rebamipide; Randomized control trial

Core tip: There is no consensus regarding the optimum period of treatment of patients with post endoscopic submucosal dissection (ESD) ulcers. 60 patients who underwent ESD for gastric cancer were randomized to two groups and treated with proton pump inhibitor for 4 wk (4W group) or 2 wk (2W group). The numbers of patients with ulcers in the healing/scar stage and the ulcer healing rate at 4 wk after ESD showed no statistical difference between 2W and 4W groups. Two-week treatment with a proton pump inhibitor is as effective as four-week treatment for healing post ESD ulcers.

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INTRODUCTION

Recently, improvements in endoscopic treatment techniques and technology have enabled the development of a new method, endoscopic submucosal dissection (ESD). ESD is a less invasive treatment for early gastric cancer than gastrectomy[1-3]. In addition, we can obtain precise histological data following ESD. After ESD, delayed bleeding, which is defined as hematemesis or melena up to 30 d after the procedure, may be treated by emergency endoscopy. The frequency of delayed bleeding varies with the tumor location and size[4,5]. Proton pump inhibitors (PPIs) are used widely to avoid delayed bleeding. PPIs have a strong effect in up-regulating gastric pH and promoting the healing of gastric ulcers, but various side effects of PPIs also have been reported, for example, pneumonia, intestinal infection, osteoporosis, and microscopic colitis[6]. In addition, most PPIs are metabolized by the cytochrome P450 pathway, specifically CYP2C19 and CYP3A3, so that combined medication with PPIs and other drugs which are metabolized by the same pathway should be undertaken with care or avoided completely[7,8].

It is difficult to identify the occurrence timing of peptic ulcers associated with *Helicobacter pylori* (*H. pylori*) infection accurately and to compare the difference in ulcer healing between the *H. pylori* infected ulcer and the artificial ulcer after ESD directly. In contrast, Hashimoto *et al*[9,10] reported that the speed of healing of artificial ulcers was faster than that of ordinary peptic ulcers and showed that the pathophysiology of artificial ulcers which form after ESD might differ from peptic ulcers associated with *H. pylori* 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 *H. pylori* infection. However, there is no consensus regarding the optimal period of PPI treatment of patients with artificial ulcers after ESD treatment. Therefore, we evaluated the optimal period of treatment of post ESD ulcers in a randomized controlled trial.

MATERIALS AND METHODS

Study design and patients

This study was a paralleled, randomized controlled trial that investigated the pharmacodynamic effect, efficacy and safety of a proton pump inhibitor in patients, following ESD treatment. Before ESD treatment, patients who were to be treated at Chiba University Hospital from January 2012 to March 2013 were recruited. Patients using antithrombotic drugs, with a tendency to bleed or on dialysis were excluded. Informed consent was obtained from all patients and this study was approved by the Ethics Committee of Chiba University Hospital (Registration number, UMIN000006951). In this study, patients with ESD were enrolled, randomized and treated with esomeprazole 20 mg per day, either for 4 wk (4W group) or 2 wk (2W group) (Figure 1). All patients received rebamipide 300 mg per day for 4 wk. Post procedure-related bleeding was recorded when hematemesis or melena were observed or the hemoglobin concentration decreased by more than 2 g/dL.

Measurement of the ulcer healing rate and speed

At 4 wk after ESD, we measured the size of the artificial ulcers by endoscopy and determined the ulcer healing rate and speed compared to the size of the ESD specimens. In addition, we calculated the ulcer healing speed (mm^2/mo) of cases in the stage of healing, that is (ESD size) - (Ulcer size at 4 wk). The primary outcome variable was the ulcer healing rate in the 2W and 4W groups.

ESD procedure

ESD was performed with a conventional single-channel endoscope (GIF-H260Z or -Q260J, Olympus, Tokyo, Japan) or 2-channel endoscope (2TQ260M, Olympus). We used an IT knife 2 (KD-611L, Olympus) and an electrosurgical current was applied with the use of an electrosurgical generator (VIO300D, ERBE). The injection solutions contained glycerin and hyaluronic acid sodium (0.4%) with 1% indigo carmine dye. The ulcers that developed after ESD were carefully examined endoscopically and any visible vessels were heat-coagulated using hemostatic forceps (FD-410LR, Olympus). Thereafter, the resected specimens were stretched, pinned flat on a cork board, and measured.

Statistical analysis

All data are represented as the mean ± SD. The unpaired *t*-test, χ^2 test, and Mann-Whitney *U* test were used for statistical analyses as appropriate with the statistical program SPSS version 21 statistical analysis package (SAS Institute, Cary, NC, United States). A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the patients after ESD treatment

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.

Ulcer healing rate of the patients after ESD treatment

Re-bleeding was observed in one patient and emergency endoscopy and endoscopic treatment was given within 2 wk of the ESD treatment. This patient was excluded from further analysis. The othes did not show post procedure-

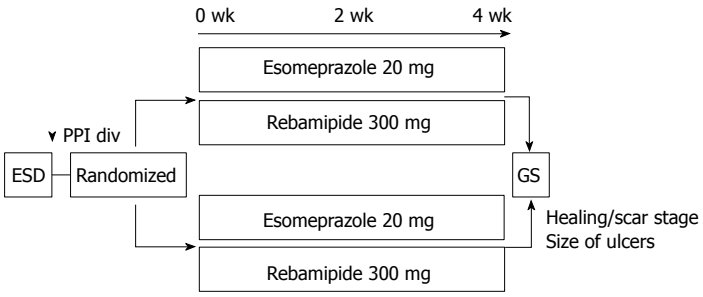

Figure 1 Study design. After endoscopic submucosal dissection, all patients were randomized to 2 wk (2W) or 4 wk (4W) group. They were administered an intravenous infusion of omeprazole 20 mg every 12 h for 1 d, and received oral esomeprazole (20 mg/d) for 2 wk or 4 wk and rebamipide at a dose of 300 mg orally, 3 times a day for 4 wk. ESD: Endoscopic submucosal dissection; PPI div: Drip intravenous infusion of proton pump inhibitor (omeprazole 40 mg/d); GS: Gastroendoscopy.

Table 1 Baseline characteristics and status of ulcer at 4 wk after endoscopic submucosal dissection

Parameter	2 wk (n = 27)	4 wk (n = 33)	P value
Clinical background			
Age (yr)	73.3 ± 7.8	70.8 ± 9.3	NS[2]
Gender (male/female)	17/10	19/14	NS[3]
Helicobacter pylori infection (+/-/unknown)	18/8/1	25/6/2	NS[3]
Location (upper/middle/lower)	3/10/14	1/14/18	NS[3]
Size of ESD (mm^2)	777.6 ± 437.8	1251.2 ± 918.6	0.048[4]
Serum albumin (g/dL)	4.1 ± 0.4	4.1 ± 0.4	NS[2]
Comorbidity			
Diabetes (+/-)	3/24	6/27	NS[3]
Hyperlipidemia (+/-)	7/20	8/25	NS[3]
Hypertension (+/-)	8/19	11/22	NS[3]
Status of ulcer at 4 wk after ESD[1]			
Stage of ulcer (active/healing/scar)	0/20/6	0/28/5	NS[2]
Ulcer healing rate (%) (average, 95%CI)	96.1 (94.6-97.5)	94.8 (92.6-97.1)	NS[3]

[1]One patient in 2 wk group who showed bleeding within 2 wk and received endoscopic treatment and proton pump inhibitor for 4 wk was excluded for these analysis; [2]Paired t-test; [3]χ^2 test; [4]Mann-Whitney U test. ESD: Endoscopic submucosal dissection; NS: No significance.

related bleeding. The numbers of patients in the ulcer healing (H)/scar (S) stage at 4 wk 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 wk 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-wk treatment compared with 4-wk treatment. The drug compliance of all patients was over 80% of the established quantity. No accumulation of adverse events for a specific symptom, disease or laboratory abnormality was observed.

Clinical characteristics in rapid healing of artificial ulcer after ESD treatment

Because the median healing area in 48 patients at the H stage at 4 wk was 968.5 mm^2, we designated this as rapid healing, that is good healing (⩾ 968.5 mm^2) in the H or S stage at 4 wk. 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 ($P = 0.049$, χ^2 test)

Table 2 Clinical characteristics of artificial ulcer after endoscopic submucosal dissection treatment with rapid healing

Parameter	Healing area in healing stage		P value
	⩾ 968.5 mm^2 (n = 24)	< 968.5 mm^2 (n = 24)	
Age (yr)	72.6 ± 8.9	68.8 ± 9.0	NS[1]
Sex (male/female)	15/9	15/9	NS[2]
Location of tumors (upper/middle/lower third)	1/11/12	1/8/15	NS[2]
Helicobacter pylori infection (+/-/unknown)	17/5/2	16/8/0	NS[2]
Initial ulcer size (mm^2)	1689.3 ± 835.7	633.5 ± 243.8	< 0.001[3]
Healing rate (%)	94.6 ± 4.5	94.0 ± 6.6	NS[3]
Treatment period (2 wk/4 wk)	7/17	13/11	NS[2]
Comorbidity			
Diabetes (yes/no)	4/20	5/19	NS[2]
Hyperlipidemia (yes/no)	3/21	7/17	NS[2]
Hypertension (yes/no)	10/14	3/21	0.0492

[1]Paired t-test; [2]χ^2 test; [3]Mann-Whitney U test. NS: No significance.

Table 3 Analysis for status of ulcer and healing area in healing stage after adjusting the size of endoscopic submucosal dissection

	2 wk (n = 17)	4 wk (n = 23)	P value
Size of ESD (mm^2)	962.2 ± 390.8	1016.2 ± 397.3	NS[1]
Ulcer healing rate (%) (average, 95%CI)	94.5 (92.7-96.3)	94.0 (91.1-96.9)	NS[1]
Ulcer healing speed in (mm^2/mo)	908.8 ± 370.6	960.7 ± 377.7	NS[1]

[1]Paired t-test; ESD: Endoscopic submucosal dissection; NS: No significance; CI: Confidence interval.

(Table 2). In contrast, age, sex, tumor location in the stomach, *H. pylori* infection, ulcer healing rate, diabetes, hyperlipidemia, and the duration of PPI treatment did not predict the speed of ulcer healing. To adjust for the difference of ESD size between 2W and 4W groups, we selected the patients who were within the range (average ± 1 SD), and the size-matched analysis was also performed (Table 3). As a result, there was no significant difference in ulcer healing rate and speed.

DISCUSSION

In previous studies, artificial ulcers that developed after ESD treatment healed within 8 wk, irrespective of size

and location[11]. However, there is no consensus regarding the optimum duration of treatment following ESD. The most frequent complication that occurs after endoscopic therapy is bleeding and the rate of intraoperative bleeding is significantly higher with ESD than with endoscopic mucosal resection. Uedo *et al*[12] indicated that PPI therapy prevented delayed bleeding from the ulcer created by ESD more effectively than did histamine H2-receptor antagonist treatment. In this study, the ratio of ulcer healing was more than 90% in both groups at 4 wk after ESD treatment. In addition, the rate of intraoperative bleeding did not differ significantly between the groups.

Oh *et al*[13] reported that the degree of healing of ESD-induced ulcers was dependent on the initial ulcer size. Kobayashi *et al*[14] reported that a larger sized ulcer after ESD was the only significant predictor of delayed healing. In this study, the factor that influenced the area of healing during the healing stage at 4 wk after ESD was the initial ulcer size, the disease rate of hypertension and not the duration of PPI treatment. In addition, the ratios of H and S stages did not differ between the 2W and 4W groups. One patient showed re-bleeding but this occurred within 2 wk and, therefore, was not related to the duration of PPI treatment. The relation between hypertension and ulcer healing is unknown and further study is needed. Using the size of ESD as a deterministic factor for randomization might improve the analysis, but in-sub-group analysis of patients whose ulcers initially were sized within the average ± 1 SD showed no significant difference in the initial size and ulcer healing rate between the 2W and 4W groups (Table 3). PPIs are a very well tolerated drug class. Their high safety, efficacy and wide distribution lead to overuse, inappropriate dosage and excessive durations of treatment. Howell *et al*[15] reported that increasing levels of pharmacologic acid suppression are associated with increased risks of nosocomial *Clostridium difficile* (CD) infection and Barletta *et al*[16] reported that the duration of PPI therapy is significantly associated with CD infection and suggested consideration of restricting PPI use, given the short exposure time. However, more recent studies have offered conflicting viewpoints regarding the association between PPI use and increased risk of CD infection[17-19]. Freedberg *et al*[20] reported that receipt of PPIs concurrent with CD treatment was not associated with recurrence of CD infection among hospitalized adults with CD, and that increased age and increased comorbidities significantly predicted recurrence. In this study, the mean age of the patients who underwent ESD treatment was over 70 years, 13 patients (22%) being 80 years of age or more, and comorbidities (diabetes, hyperlipidemia, and hypertension) often were observed. In addition, PPIs are metabolized by the cytochrome P450 pathway, specifically CYP2C19 and CYP3A3. Clopidogrel, which is used to inhibit blood clots, requires biotransformation for conversion to its active form, mediated by the enzymes CYP2C19 and CYP3A3[21]. The Food and Drug Administration in the United States issued a recommendation against the combined use of clopidogrel and specific PPIs (potent CYP2C19 inhibitors). Therefore, it is not desirable to use PPIs blindly for a long period and we have to define the optimized period of PPI use, especially for patients with a past history of CD infection, pneumonia or use of clopidogrel.

In this study, all patients were treated with rebamipide for 4 wk. Rebamipide has been reported to induce healing of ulcers, especially artificial ulcers[14]. Nishizawa *et al*[22] reported that the administration of rebamipide could induce the expression of Sonic Hedgehog (Shh) and we also reported that the expression level of Shh in the gastric mucosa showed a good correlation with the speed of healing of artificial ulcers[23], that is, rebamipide could promote the healing of ulcers *via* Shh, which could influence some cellular and tissue functions, including cell proliferation and tissue repair[24,25]. The use of rebamipide might eliminate the distinction in healing rate between the 2W and 4W groups. But, in our previous report, we treated 45 artificial ulcers after ESD only by PPI (esomeprazole or omeprazole) for 4 wk 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[23]. This result suggested us that the effect of adding rebamipide on healing ulcer was limited.

In conclusion, two-week treatment with PPI is as effective as four-week treatment for healing post ESD ulcers. In view of the results of this study, we could shorten the period of PPI treatment for artificial ulcers after ESD.

COMMENTS

Background

Endoscopic submucosal dissection (ESD) is a less invasive treatment for early gastric cancer than gastrectomy. Proton pump inhibitors (PPIs) are used widely to avoid delayed bleeding. PPIs have a strong effect in up-regulating gastric pH and promoting the healing of gastric ulcers, but various side effects of PPIs also have been reported, for example, pneumonia, intestinal infection, osteoporosis, microscopic colitis and drug interaction.

Research frontiers

The pathophysiology of artificial ulcers which form after ESD might differ from peptic ulcers associated with *Helicobacter pylori* infection. However, there is no consensus regarding the optimal period of PPI treatment of patients with artificial ulcers after ESD treatment.

Innovations and breakthroughs

Two-week treatment with PPI is as effective as four-week treatment for healing post ESD ulcers.

Applications

We can shorten the period of PPI treatment for artificial ulcers after ESD. It can avoid the side effects of PPI.

Terminology

Cytochrome P450 (CYP): By the CYP pathway, various drugs are metabolized. Most PPIs are metabolized by the cytochrome P450 pathway, specifically CYP2C19 and CYP3A3.

Peer review

There was no study to evaluate the optimal period of PPI treatment for the artificial ulcer after ESD by a prospective, randomized trial. This study is the first report to show the possibility to shorten the period of PPI treatment.

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