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Effect of ilaprazole on the healing of endoscopic submucosal dissection-induced gastric ulcer: randomized-controlled, multicenter study

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Abstract

Background The optimal treatment regimen or the duration of treatment for an endoscopic submucosal dissection (ESD)-induced gastric ulcer has not been established. The aim of this study was to assess the efficacy of novel proton-pump inhibitor, ilaprazole, for the treatment of ESD-induced gastric ulcer.

Methods This was a prospective, open-label, randomized multicenter study. Between June 2015 and March 2018, a total of 176 patients (178 lesions) who underwent ESD for a gastric neoplasm were randomly allocated to receive the oral proton-pump inhibitor ilaprazole 20 mg or rabeprazole 20 mg daily for 8 weeks. The primary outcome was the ulcer healing rate at 4 and 8 weeks.

Results A total of 155 (157 lesions) and 154 patients (156 lesions) were included in the modified intention-to-treat (mITT) and per-protocol analyses, respectively. There was no significant difference in the ulcer healing rate (ilaprazole vs. rabeprazole, 97.4% vs. 97.0 $p=0.78$ at 4 weeks, 100% vs. 100%, $p=0.95$ at 8 weeks in the mITT analysis) or stage of ulcer (scar stage, 25.6% vs. 17.7%, $p=0.25$ at 4 weeks, 92.3% vs. 88.6%, $p=0.59$ at 8 weeks in the mITT analysis) between the treatment groups. The quality of ulcer healing was not significantly different between the two groups. No independent predictive factor for higher-quality ulcer healing was found in the multivariate analysis.

Conclusions According to this trial, ilaprazole and rabeprazole showed no significant difference in the healing of artificial gastric ulcers. Most of the ulcers achieved complete healing within 4–8 weeks. Trial registration: ClinicalTrial.gov NCT02638584.

Keywords Gastric ulcer · Endoscopic submucosal dissection · Ilaprazole · Rabeprazole · Endoscopy

Abbreviations

ESD	Endoscopic submucosal dissection
PPI	Proton-pump inhibitor
H. pylori	*Helicobacter pylori*
KGSRS	Korean form of Gastrointestinal Symptom Rating Scale
mITT	Modified intention-to-treat
PP	Per-protocol
IQR	Interquartile range
SD	Standard deviation
OR	Odds ratio
CI	Confidence interval
n	Number
BMI	Body mass index

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Endoscopic submucosal dissection (ESD) has been established as a primary treatment option for a specific subset of patients with gastric neoplasms who have a negligible risk of lymph node metastasis [1, 2]. With technical advancements, treatment outcomes in patients with gastric neoplasms who meet the criteria for endoscopic resection have reached a level comparable to those of surgical resection [3, 4]. ESD

has the advantage of an en bloc resection of neoplastic tissue and is less invasive than surgery because the stomach is preserved if curative resection is achieved. However, to achieve clear resection margins, this procedure inevitably leaves a large and deep ulcer, which can lead to major complications. Hemorrhage of the ESD-induced ulcer is immediately treated during the procedure; however, delayed bleeding is also a drawback of ESD [1]. Proton-pump inhibitors (PPIs) are the most widely used anti-ulcer medication and are currently the standard treatment, not only in patients with peptic ulcers but also in patients with ESD-induced artificial gastric ulcers. We previously reported that a combination therapy of oral PPI and rebamipide, a mucosa-protective agent, for 4 weeks is more effective than oral PPI monotherapy in terms of the healing rate and quality of healing of ESD-induced gastric ulcers [5]. However, the optimal treatment regimen (intravenous vs. oral, continuous infusion vs. intermittent injections, once daily vs. twice daily, etc.) or duration of treatment for ESD-induced gastric ulcers has not been established.

Ilaprazole (Noltec®; IL-YANG Pharmaceutical Co., Ltd., Seoul, Korea) has a prolonged plasma half-life compared to other available PPIs and is not significantly influenced by *CYP2C19* polymorphisms, which limits the efficacy of a PPI [6, 7]. This medication is also known to provide better pH control over 24 h without plasma gastrin concentration elevation compared with esomeprazole [8]. Rabeprazole, which is a 2nd-generation PPI like esomeprazole, was reported to have a stronger acid suppressing efficacy than 1st-generation PPIs [8, 9]. It is also less affected by *CYP2C19* polymorphisms, which is more prevalent in East Asian countries than Western countries [10]. Although there are theoretical advantages of these drugs, the comparative efficacy of ilaprazole with rabeprazole for the treatment of ESD-induced artificial gastric ulcers has not been evaluated. Therefore, we assessed the comparative efficacy of ilaprazole and rabeprazole for the treatment of ESD-induced gastric ulcers.

Methods

Study population

Patients who underwent ESD for the treatment of gastric adenoma or early gastric cancer from June 2015 to March 2018 at the Hallym University-Affiliated Hospitals, including the Chuncheon, Kangdong, and Dongtan Sacred Heart Hospital were enrolled. Inclusion criteria were as follows: (1) 19 years of age or older; (2) pathologically diagnosed gastric adenoma or cancer that was eligible for ESD [11, 12]; and (3) agreed to participate and voluntarily provided informed consent. Exclusion criteria were as follows: (1) known hypersensitivity to any component of ilaprazole; (2) taking a medication contraindicated with experimental and concomitant drugs; (3) abnormal levels of laboratory tests (serum total bilirubin or creatinine > 1.5 times the upper limit of normal and alanine transaminase, aspartate transaminase, alkaline phosphatase, and blood urea nitrogen > 2 times upper limit of normal); (4) history of malignancy within 5 years other than gastric cancer; (5) history of Zollinger-Ellison syndrome, Barrett's esophagus, primary esophageal motility abnormality, esophageal strictures, pancreatitis, malabsorption, severe cardiovascular or pulmonary disease; (6) history of major surgery that can affect gastric acid secretion; (7) cannot discontinue the following medications during the study period: anticholinergics, motility-promoting agents, prostaglandin analogs, sucralfate, aspirin, steroids, and nonsteroidal anti-inflammatory drugs; (8) uncontrolled organ failure (liver dysfunction or renal dysfunction); and (9) pregnant and/or breast feeding women.

Study design

This was a prospective, open-label, randomized multicenter study. Sample size was calculated by using an α-error < 0.05 and a β-error < 0.2 with a two-tailed significance test. The calculated number of lesions required for the study was 70 in each arm, determined by assuming a healing rate of 87% over 8 weeks of treatment with a 2nd-generation oral PPI based on a previous study, a non-inferiority margin of 15%, and a drop rate of 10% [13]. All patients were given intravenous injections of pantoprazole 40 mg on the first 2 days after ESD. Oral feeding was initiated on the second day after performing the 2nd-look endoscopy to check for post-ESD hemorrhage. Patients with bleeding resumed their diet after confirming complete hemostasis. On the third day, the patients who met the inclusion and exclusion criteria were randomly assigned to the ilaprazole or the rabeprazole group. A single independent study coordinator prepared the randomization sequence, which was accomplished by using a block design with a block size of 4. Randomization of the block was conducted using a random-number chart.

Beginning on the third day after ESD, the patients in the ilaprazole group were administered ilaprazole 20 mg oral tablets once a day for 56 days, and the patients in the rabeprazole group were administered rabeprazole 20 mg oral tablets once a day for 56 days. The enrolled patients underwent follow-up endoscopy at 4 weeks and 8 weeks after ESD to evaluate the degree and quality of ulcer healing. Adverse events and drug compliance were evaluated at 4 weeks and 8 weeks. The visit window was 1 week. *Helicobacter pylori* (*H. pylori*) infection was evaluated by histopathologic examination, rapid urease test (Pronto Dry New®; Medical Instruments Corp., Herford, Germany), and/or the ^{13}C-urea breath test (HeliFinder cap®; MediChems Corp., Seoul, Korea)

before performing the ESD. We defined *H. pylori* infection as positive when at least one of the tests showed positivity. All enrolled patients were asked to complete the modified Korean form of the Gastrointestinal Symptom Rating Scale (KGSRS) to evaluate the change in clinical symptoms before and after performing ESD [14, 15]. KGSRS is a rating scale consisting of 15 parameters and is widely used to assess abdominal symptoms in patients with peptic ulcers.

The study protocol adhered to the ethical guidelines established by the 1975 Declaration of Helsinki and received approval by the Ministry of Food and Drug Safety and the institutional review board for human research at each hospital before the study was initiated (number: 2015-64). This study was also registered at *ClinicalTrial.gov* (Clinical trial registration number, NCT02638584). Informed consent to participate in the study was voluntarily obtained from each patient.

Standardization of ESD

Indications of ESD were as follows: (1) gastric adenoma regardless of size that had an anticipated incomplete or difficult resection using conventional endoscopic mucosal resection; (2) differentiated-type mucosal adenocarcinoma without ulceration and lymphovascular invasion irrespective of size; (3) differentiated-type mucosal adenocarcinoma ≤ 30 mm with ulceration and without lymphovascular invasion; and (4) differentiated-type adenocarcinoma ≤ 30 mm with minute submucosal invasion (depth of invasion of ≤ 500 μm) but without lymphovascular invasion [11, 12]. ESD procedures were performed using standard techniques (marking, submucosal injection, incision, submucosal dissection, and hemostasis). Patients were sedated with a continuous infusion of propofol. After marking the extent of resection on the normal mucosa surrounding the tumor using electrocautery, the submucosa was injected with a mixture of 0.9% saline, 0.2% indigo carmine, and 1:10,000 diluted epinephrine solution or hyaluronic acid solution (Endo-Ease®; Unimed Pharmaceutical Inc., Seoul, Korea) to lift the gastric neoplasm. We performed a circumferential incision and submucosal dissection using suitable knives, such as a needle-type knife or an insulation-tipped knife. Hemostatic forcep (FD411QR; Olympus Co., Ltd., Tokyo, Japan) or an argon plasma coagulation probe (E120689; ERBE Co., Ltd, Tübingen, Germany) was used for hemostasis during or after ESD. The resected specimen was immediately fixed on a polystyrene plate with 10% formalin and sent for pathologic diagnosis.

Study outcomes

The primary outcome was the ulcer reduction rate at 4 and 8 weeks after ESD, which was calculated as follows: [(initial ulcer area − ulcer area at 4 or 8 weeks) × 100/initial ulcer area]. The maximum diameter and the largest diameter perpendicular to the maximum diameter of the ulcer were measured using an endoscopic measuring device (M2-3U®; Olympus Co., Ltd., Tokyo, Japan). Ulcerated areas were calculated by multiplying these two diameters. The secondary outcomes were change in ulcer stage, quality of ulcer healing, change in clinical symptoms, and whether healing was delayed after ESD.

Ulcer stage was evaluated using the classification of Sakita and Fukutomi, described as active (A1, A2), healing (H1, H2), and scarring (S1, S2) [16]. Two endoscopic experts blinded to patient information (W.G.S and G.H.B) assessed the quality of ulcer healing by reviewing chromoendoscopic photographs with the use of indigo carmine (100 randomly selected chromoendoscopic photographs by a single independent study coordinator using a random-number chart). They reported the presence of flat (high quality of ulcer healing) or nodular (low quality of ulcer healing) lesions as previously described [5]. The sum of the scores of each parameter in the KGSRS ranges from 0 to 39 with higher score indicating severe gastrointestinal symptoms [14]. Post-ESD delayed bleeding was defined as an active ulcer with acute hemorrhage occurring from day 2 to day 56 that satisfies one of the following criteria: (1) hematemesis, melena, or hematochezia that requires endoscopic hemostasis; (2) systolic blood pressure ≤ 90 mmHg or pulse rate ≥ 110/min; (3) decreased level of serum hemoglobin by > 2 g/dl or hematocrit by > 6% and serum hemoglobin < 10 g/dl; and (4) definitively observed active hemorrhage, blood clots, or exposed vessels on endoscopic examination after performing ESD.

Statistical analysis

If enrolled patients had more than one gastric lesion for ESD, each lesion was assumed to constitute statistically independent observations for the purposes of data analysis. For the modified intention-to-treat (mITT) analysis, all patients excluding those lost to follow-up or those who underwent an additional operation after ESD (due to the resection margin positive) were included and analyzed. For the per-protocol (PP) analysis, only those who maintained and completed treatment with the prescribed medications without violating the regulations (< 80% medication compliance) were included and assessed.

The Kolmogorov–Smirnov and Shapiro–Wilk tests were conducted to determine whether or not each continuous variable was normally distributed. Non-parametric continuous variables were expressed as the median and interquartile range (IQR). Parametric continuous variables were expressed as the mean ± standard deviation (SD). Categorical variables were expressed as frequencies

and percentages. The Mann–Whitney test was used to compare non-parametric continuous variables and the student's *t* test was used to compare normally distributed continuous variables. The Fisher's exact test was used to compare categorical variables.

First, we compared the differences in the baseline characteristics of the enrolled population. Then, we performed mITT and PP analyses to compare ulcer healing rates between the two arms. A multivariable logistic regression test was performed to detect the independent predictive factors for higher-quality ulcer healing. The Cohen's kappa coefficient was used to determine the degree of agreement between two endoscopists in assessing quality of ulcer healing. Interpretation of kappa values are as follows: poor (below 0), slight (0.01–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80), and perfect (0.81–0.99) agreement [17]. In the present study, a p value < 0.05 (two-tailed) was used as the threshold for statistical significance for all tests. All of the analyses were performed using SPSS version 22.0. (SPSS Inc., Chicago, IL, USA). All of the authors had access to the data and reviewed and approved the final manuscript.

Results

Baseline characteristics

Of the 181 eligible patients initially enrolled in this study, five patients who did not meet the inclusion criteria (could not discontinue aspirin or nonsteroidal anti-inflammatory drugs) were excluded. A total of 176 patients (178 lesions) were randomly allocated to the ilaprazole group ($n = 88$) or the rabeprazole group ($n = 88$). Among them, 15 patients were lost to follow-up and 6 patients underwent an additional operation due to a positive resection margin after ESD. As a result, a total of 155 patients [(157 lesions), ilaprazole group ($n = 77$) and rabeprazole group ($n = 78$)] were included in the mITT analysis. During the study period, one patient was excluded due to violation of the protocol. Ultimately, 154 patients [(156 lesions), ilaprazole group ($n = 77$) and rabeprazole group ($n = 77$)] were eligible for the PP analysis. A detailed study flow diagram is shown in Fig. 1. There was no significant difference in terms of the demographic characteristics (age, sex, alcohol, smoking, and body mass index), endoscopic characteristics (histopathology, location of the lesion, tumor with scar, diameter of the lesion, and depth of invasion), procedure-related characteristics (rate of en bloc

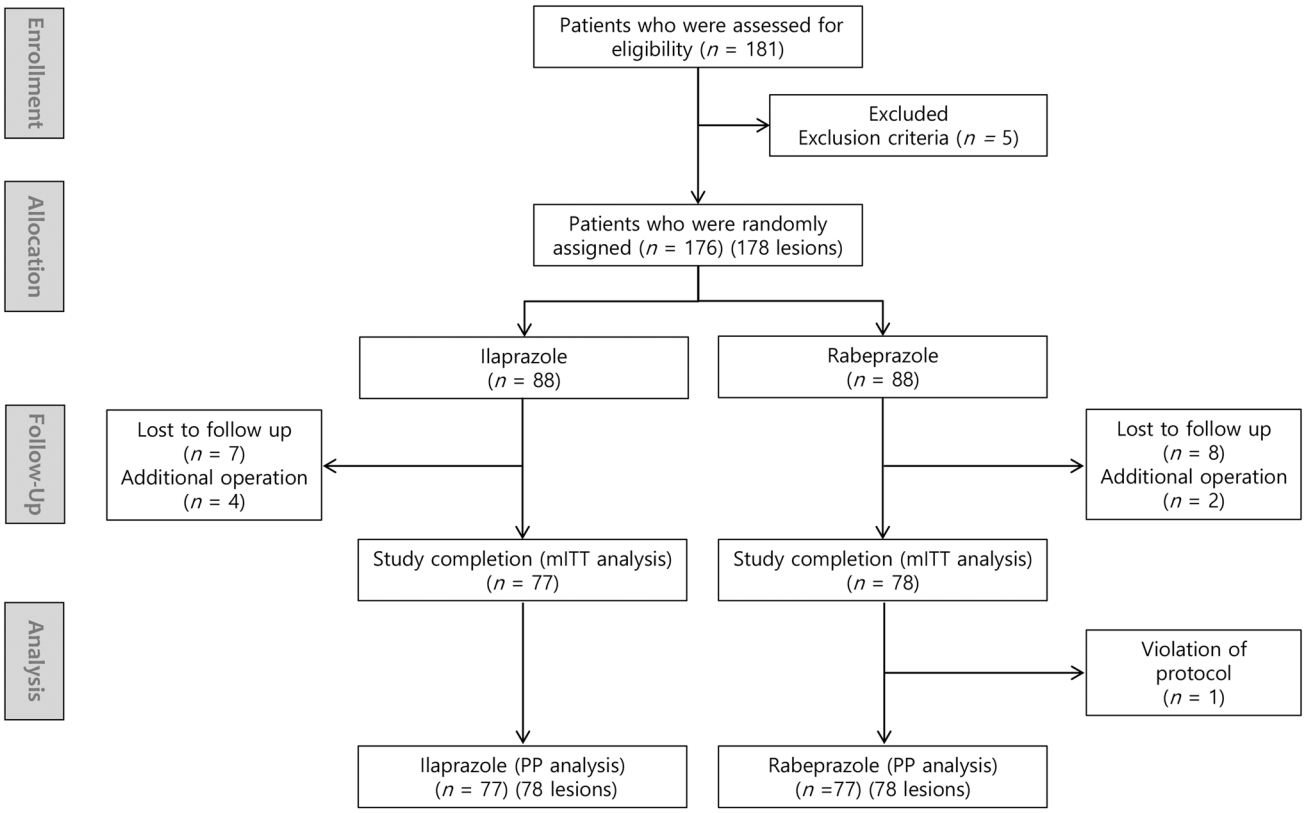

Fig. 1 Flow chart of the study

resection, complete resection, post-ESD delayed bleeding and procedure time), and general medical conditions (pervious peptic ulcer history, diabetes, hypertension, *H. pylori* infection, and gastrointestinal symptoms) (Table 1).

Ulcer healing rate at 4 weeks and 8 weeks after ESD

The median ulcer healing rate at 4 weeks and 8 weeks was 97.1% (IQR 94.5–98.7%) and 100% (IQR 99.5–100%), respectively. There was no significant difference in the ulcer healing rate between the ilaprazole and rabeprazole groups (97.4% vs. 97.0%, $p=0.78$ at 4 weeks) (100% vs. 100%, $p=0.95$ at 8 weeks) in the mITT analysis, and this was also consistent (97.4% vs. 97.0%, $p=0.86$ at 4 weeks, 100% vs. 100%, $p=0.90$ at 8 weeks) in the PP analysis. The proportion of scarring stage ulcers was not significantly different between each treatment group (25.6% vs. 17.7%, $p=0.25$ at 4 weeks, 92.3% vs. 88.6%, $p=0.59$ at 8 weeks) in the mITT analysis, and this was also consistent (25.6% vs. 17.9%, $p=0.33$ at 4 weeks, 92.3% vs. 88.5%, $p=0.59$ at 8 weeks) in the PP analysis (Table 2).

Predictive factor for a higher rate of ulcer healing

We evaluated the independent predictive factors for a higher rate of ulcer healing. A higher rate of ulcer healing was defined as higher than the average healing rate observed in this trial (94.7% at 4 weeks and 99.0% at 8 weeks). Univariate analysis revealed that no factor was significant for a higher ulcer healing rate at 4 weeks and 8 weeks. The

Table 1 Baseline characteristics of enrolled population

Variables	Ilaprazole ($n=78$)	Rabeprazole ($n=79$)	p value
Age [median (IQR)]	62 (55.8–70)	64 (56–73)	0.35
Sex (male/female)	62/16	51/28	0.05
Alcohol [*n* (%)]	34 (43.6%)	28 (35.4%)	0.33
Smoking [*n* (%)]	19 (24.4%)	18 (22.8%)	0.85
Previous peptic ulcer [*n* (%)]	9 (11.5%)	13 (16.5%)	0.49
Pre-ESD histopathology [*n* (%)]			
Adenoma	66 (84.6%)	69 (87.3%)	0.65
Carcinoma	12 (15.4%)	10 (12.7%)	
Post-ESD histopathology [*n* (%)]			
Adenoma	56 (71.8%)	55 (69.6%)	0.86
Carcinoma	22 (28.2%)	24 (30.4%)	
Location [*n* (%)]			
Antrum	52 (66.7%)	46 (58.2%)	0.48
Angle	12 (15.4%)	11 (13.9%)	
Upper body	2 (2.6%)	5 (6.3%)	
Lower body	12 (15.4%)	17 (21.5%)	
Tumor with scar [*n* (%)]	1 (1.3%)	1 (1.3%)	> 0.99
Long diameter of tumor [median (IQR), mm]	12 (8–16)	10 (10–18)	0.67
Specimen size after fixation [median (IQR) (mm^2)]	503 (109–965)	500 (150–875)	0.96
Diabetes [*n* (%)]	18 (23.1%)	15 (19%)	0.56
Hypertension [*n* (%)]	29 (37.2%)	29 (36.7%)	> 0.99
En bloc resection rate (%)	76 (97.4%)	76 (96.2%)	> 0.99
Complete resection rate (%)	77 (98.7%)	78 (98.7%)	> 0.99
Depth of invasion, submucosa involvement [*n* (%)]	2 (2.6%)	4 (5.1%)	0.68
Procedure time [median (IQR), min]	28.5 (18.8–40)	26 (18–38)	0.23
Post ESD delayed bleeding	3 (3.8%)	5 (6.4%)	0.72
Baseline symptom score [median (IQR)]	1 (0–3)	1 (0–4)	0.51
Symptom score at 4 weeks [median (IQR)	1 (0–3)	1 (0–4)	0.67
Symptom score at 8 weeks [median (IQR)]	1 (0–2.3)	1 (0–3)	0.81
Helicobacter pylori infection [*n* (%)]	38/73 (52.1%)	33/68 (48.5%)	0.74
BMI[a] (mean ± SD)	24.7 ± 3.8	25.0 ± 2.9	0.63

n number, *IQR* interquartile range, *SD* standard deviation, *ESD* endoscopic submucosal dissection, *BMI* body mass index

[a]Student's *t* test was used

Table 2 Ulcer healing rate at 4 weeks and 8 weeks after ESD

Variable	Modified intension-to-treat analysis			Per-protocol analysis		
	Ilaprazole ($n=78$)	Rabeprazole ($n=79$)	p value	Ilaprazole ($n=78$)	Rabeprazole ($n=78$)	p value
Area of ulcer [median (IQR) (mm^2)]						
Initial	1000 (900–1581.3)	1050 (800–1575)	0.99	1000 (900–1581.3)	1050 (856.3–1581.3)	0.92
4 weeks after ESD	36 (15–70.5)	36 (15–64)	0.86	36 (15–70.5)	36 (15.8–66)	0.93
8 weeks after ESD	0 (0–6)	0 (0–12)	0.93	0 (0–6)	0 (0–12)	0.88
Healing rate at 4 weeks [median (IQR), %]	97.4 (93.9–98.8)	97 (94.6–98.4)	0.78	97.4 (93.9–98.8)	96.9 (94.7–98.4)	0.86
Healing rate at 8 weeks [median (IQR) %]	100 (99.6–100)	100 (99.2–100)	0.95	100 (99.6–100)	100 (99.2–100)	0.90
Scar stage at 4 weeks [n (%)]	20 (25.6%)	14 (17.7%)	0.25	20 (25.6%)	14 (17.9%)	0.33
Scar stage at 8 weeks [n (%)]	72 (92.3%)	70 (88.6%)	0.59	72 (92.3%)	69 (88.5%)	0.59

n number, *IQR* interquartile range, *ESD* endoscopic submucosal dissection

multivariate analysis adjusting for factors with $p<0.5$ in the univariate analysis revealed that no factor was significant for a higher ulcer healing rate at 4 weeks and 8 weeks (Table 3).

Quality of ulcer healing

The quality of ulcer healing reviewed by two expert endoscopists was not significantly different between the ilaprazole group and rabeprazole group [reviewer 1; odds ratio (OR): 1.63, 95% confidence interval (CI): 0.68–3.91, $p=0.38$, reviewer 2; OR 1.41, 95% CI 0.55–3.59, $p=0.64$]. The Cohen's kappa coefficients for the determination of the quality of ulcer healing between the two endoscopists was 0.74, indicating substantial agreement (Table 4).

Clinical symptoms and delayed bleeding after ESD

The clinical symptom scores between the ilaprazole and rabeprazole groups were not significantly different at baseline, 4 weeks, and 8 weeks after ESD (p vales: 0.51, 0.67, and 0.81, respectively). There was no case of ESD-induced gastric perforation. Only eight cases of delayed bleeding (5.2%) were noted, and the rate of delayed bleeding was not significantly different between the two groups (3.8% vs. 6.4%, $p=0.72$) (Table 1).

Discussion

Previous studies have evaluated the efficacy of PPIs versus histamine two receptor blockers [18], PPIs with additive mucoprotective agents such as rebamipide or ecabet sodium versus PPI monotherapy [5, 19, 20], or 2nd -generation PPIs with rebamipide vesrus 1st -generation PPIs with rebamipide [21] in terms of healing of ESD-induced artificial gastric ulcers. However, head-to-head comparisons of a 2nd -generation PPI monotherapy for the efficacy of healing in artificial gastric ulcers have been scarce. Ilaprazole is mainly metabolized by *CYP3A4*, and rabeprazole mainly undergoes non-enzymatic metabolism and is also less dependent on *CYP2C19* polymorphism [6, 22]. In our trial, these PPIs, which have already shown better efficacy on peptic ulcers compared to other 1st -generation PPIs, showed no significant difference in the healing of artificial gastric ulcers [23, 24].

The mechanism of healing in ESD-induced gastric ulcers is different from that of a peptic ulcer. In contrast to the peptic ulcer in which the proper muscle layer is damaged by inflammation and replaced by scar tissue, the iatrogenic ulcer usually has normal contractility with an intact proper muscle layer [25]. Therefore, the healing process is facilitated mostly by muscular contractions with strong traction towards the ulcer center with little regenerative mucosa and microcirculation restoration with granulation tissue formation [26–30]. The pathogenic mechanism is completely mechanical; therefore, mucosal damage by gastric acid or digestive enzymes and cellular apoptosis by *H. pylori* are not the main related factors [27]. The stomach is usually under hypoacidic conditions due to periprocedural PPI injections and the normal mucosal protective mechanism is intact in patients who undergo gastric ESD. Therefore, ESD-induced artificial gastric ulcers usually heal within 8 weeks regardless of the size and location of the lesion, *H. pylori* infection status, or the extent of gastric atrophy [25, 27].

Nonetheless, studies have investigated the associated factors for delayed ulcer healing because the details of the healing process have not been completely understood and delayed healing continues to be a common complication of gastric ESD [26, 29–31]. One of the factors that has shown inconsistent results is the location of the lesion. Kobayashi et al. reported that the healing rate of the artificial ulcer in the antrum is higher than that of the body because of

Table 3 Independent predictors for higher than average ulcer healing at 4 weeks and 8 weeks after ESD

Variable	Univariate analysis (at 4 weeks)			Univariate analysis (at 8 weeks)		
	Ulcer healing < 94.7% ($n=45$)	Ulcer healing ≥ 94.7%* ($n=111$)	p value	Ulcer healing < 99.0% ($n=31$)	Ulcer healing ≥ 99.0%* ($n=125$)	p value
Age [median (IQR)]	63 (56.5–74)	62 (56–70)	0.60	62 (55–73)	62 (56–72)	0.80
Ilaprazole vs. rabeprazole	25 (55.6%) vs 20 (44.4%)	53 (47.7%) vs. 58 (52.3%)	0.48	13 (41.9%) vs 18 (58.1%)	65 (52.0%) vs. 60 (48.0%)	0.42
Sex (male/female)	29/16	83/28	0.24	19/12	93/32	0.18
Alcohol [*n* (%)]	16 (35.6%)	45 (40.5%)	0.59	14 (45.2%)	47 (37.6%)	0.54
Smoking [*n* (%)]	9 (20%)	28 (25.2%)	0.54	6 (19.4%)	31 (24.8%)	0.64
Previous peptic ulcer [*n* (%)]	6 (13.3%)	16 (14.4%)	> 0.99	5 (16.1%)	17 (13.6%)	0.77
Post-ESD histopathology [*n* (%)]						
Adenoma	35 (77.8%)	75 (67.6%)	0.25	23 (74.2%)	87 (69.6%)	0.67
Carcinoma	10 (22.2%)	36 (32.4%)		8 (25.8%)	38 (30.4%)	
Location [*n* (%)]						
Antrum	25 (60.0%)	70 (63.1%)	0.91	18 (58.1%)	79 (63.2%)	0.33
Angle	6 (13.3%)	17 (15.3%)		4 (12.9%)	19 (15.2%)	
Upper body	2 (4.4%)	5 (4.5%)		0 (0%)	7 (5.6%)	
Lower body	10 (22.2%)	19 (17.1%)		9 (29.0%)	20 (16.0%)	
Tumor with scar [*n* (%)]	0 (0%)	2 (1.8%)	> 0.99	1 (3.2%)	1 (0.8%)	0.36
Initial area of ulcer [median (IQR), mm^2]	900 (870–1450)	1200 (875–1600)	0.23	1200 (600–1575)	1050 (900–1587.5)	0.70
Diabetes [*n* (%)]	10 (22.2%)	22 (19.8%)	0.83	10 (32.3%)	22 (17.6%)	0.08
Hypertension [*n* (%)]	12 (26.7%)	46 (41.4%)	0.10	12 (38.7%)	46 (36.8%)	0.84
Depth of invasion, submucosa involvement [*n* (%)]	1 (2.2%)	5 (4.5%)	0.67	0 (0%)	6 (4.8%)	0.60
Procedure time [median (IQR), min]	26 (19.5–37.5)	26 (17–40)	0.75	30 (20–45)	26 (17–37.5)	0.18
Symptom score [median (IQR)]	1 (0–4.5)	1 (1–3)	0.42	0 (0–3)	1 (0–3)	0.51
Helicobacter pylori infection [*n* (%)]	19/41 (46.3%)	50/98 (51.0%)	0.71	11/28 (39.3%)	58/111 (52.3%)	0.29
BMI[a] (mean ± SD)	24.5 ± 4.2	25.0 ± 3.0	0.41	24.6 ± 3.6	24.9 ± 3.3	0.61

n number, *IQR* interquartile range, *SD* standard deviation, *ESD* endoscopic submucosal dissection

*The average healing rate of this trial (94.7% at 4 weeks and 99.0% at 8 weeks)

[a]Student's *t* test was used

Table 4 Quality of ulcer healing after ESD

Quality of ulcer healing	Ilaprazole ($n=50$)	Rabeprazole ($n=50$)	p value	OR	95% CI		Kappa value
					Lower	Upper	
Reviewer 1							0.74
Flat	38 (76%)	33 (66%)	0.38	1.63	0.68	3.91	
Nodular	12 (24%)	17 (34%)					
Reviewer 2							
Flat	40 (80%)	37 (74%)	0.64	1.41	0.55	3.59	
Nodular	10 (20%)	13 (26%)					

n number, *IQR* interquartile range, *ESD* endoscopic submucosal dissection

the ease of mucosal contraction [28]. However, Shimozato et al. reported that the lower third of the stomach is associated with delayed healing because of stronger peristalsis than other locations [29]. Lim et al. and Niimi et al. showed that the middle third and the lesser curvature of the stomach is associated with delayed healing in univariate analyses, respectively [31, 32]. The presumed mechanism was extensive use of electrocoagulation due to abundant submucosal vasculature including perforating vessels from the proper muscle layer and longer procedure time than other locations [31]. Another possible mechanism is the lack of the medial longitudinal oblique muscle bundles in the lesser curvature of the corpus, making it vulnerable to kinetic strain [32]. However, the location of the lesion was not a significant predictor for the higher healing rate in our study and this was consistent in the previous study by Kakushima et al. [33]. The presumed mechanism is due to the relatively high acid inhibitory effect of ilaprazole or rebeprazole compared to other 1st generation PPIs and more angiogenesis promotion due to persistent use of the PPI for 8 weeks [9].

Other factors for delayed healing from previous reports include fibrosis of the submucosal layer of the lesion, longer procedure time, and proper muscle damage by electrocoagulation [5, 30]. All of these factors are clear causes of delayed healing. However, these findings were not shown in our study because novice endoscopists did not perform ESD in our study and only 1.3% of patients had submucosal fibrosis in the gastric lesion. Therefore, the procedure time was much shorter than our previous study (median 26 min in the current study vs. 56.7 min in the previous study) [5] and proper muscle damage by electrocoagulation was expected to be small.

In terms of delayed bleeding after ESD, 5.2% of patients showed delayed bleeding, which is not different from those of previous reports (2.6–7%) [1, 26, 29]. With expanding indications for ESD, the risk of delayed bleeding from ESD-induced ulcers is increasing [34]. Previous studies reported that size of the lesion > 20 mm or diameter of resected specimen > 40 mm was associated with delayed bleeding [35, 36]. However, these factors were not found to be significant in our study ($p > 0.99$, not illustrated in the result section). The presumed mechanism is due to the relatively high acid inhibitory effect of ilaprazole or rebeprazole and persistent use during the entire study period. Considering most of the ESD-induced hemorrhage occurs within 28 days after ESD, the recommended duration of the PPI therapy should be at least 4 weeks [35]. However, this remains controversial because delayed healing was not related to severe adverse outcomes [32].

Additive treatment with PPI for promoting healing of ESD-induced artificial ulcers has been thoroughly investigated in studies including our previous report [5, 19]. Rebamipide, which induces the up-regulation of epidermal growth factor, maintains gastric mucosal integrity by increasing prostaglandin concentration and mucosal blood flow [19, 34]. Previous studies indicated that PPI monotherapy was insufficient in healing artificial gastric ulcers with severe gastric atrophy or large ulcers (resected specimen area ≥ 1200 mm^2) [28, 37]. Gastric atrophy was not measured in our study and only 16.7% of the resected specimens showed an area > 1200 mm^2. Therefore, in our study, PPI monotherapy appeared sufficient for ulcer healing due to the relatively high acid inhibitory effect and the persistent use of the PPI.

In terms of the dosage or duration of PPIs, inconsistent results have been reported due to the difference in study design or insufficient statistical power of the studies. Park et al. reported that a half dose of rabeprazole for 4 weeks showed sufficient ulcer healing [38]. Studies on potassium-competitive acid blockers, which show stronger antisecretory effects compared to PPIs, have shown inconsistent results indicating that acid suppression is not the only required factor for iatrogenic ulcer healing and prevention of delayed bleeding [29, 39–44]. Studies regarding duration of PPI therapy have also shown various results; in one study, even a single-week treatment with a PPI was sufficient to achieve artificial ulcer healing [45].

Considering the factors stated above, a tailored treatment strategy based on risk factors of delayed healing of artificial gastric ulcers is recommended. The combination of mucosal protective drugs with a PPI should be recommended in lesions with proper muscle damage, lesions with fibrosis of the submucosal layer, or lesions requiring longer procedure time. Lesions without these risk factors can be considered for a lower dose or a shorter duration of PPI treatment.

In conclusion, ilaprazole and rabeprazole showed no significant difference in the healing of artificial gastric ulcers, and most of the ulcers achieved complete healing within 4–8 weeks.

Author contributions WGS: Conception and design of the study. CSB, WGS, SIS, MHC, HJJ, SPS, YJY, GHB, HYK: Generation, collection, assembly, analysis and/or interpretation of data. CSB: Drafting or revision of the manuscript. WGS: Approval of the final version of the manuscript.

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Compliance with ethical standards

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