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Comparison of the Efficacy of Polaprezinc Plus Proton Pump Inhibitor and Rebamipide Plus Proton Pump Inhibitor Treatments for Endoscopic Submucosal Dissection-induced Ulcers

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Goals: We assessed the efficacy of polaprezinc plus proton pump inhibitor (PPI) treatment for endoscopic submucosal dissection (ESD)-induced ulcer healing compared with rebamipide plus PPI treatment.

Background: ESD has been widely used as a local treatment option that cures gastric neoplasms. However, it causes large and deep artificial ulcers, and there are no guidelines with regard to the optimal treatment durations and drug regimens for ESD-induced ulcers. Polaprezinc is effective for promoting ulcer healing and helps enhance the quality of ulcer healing.

Study: Two hundred ten patients with ESD-induced ulcers were randomly allocated to treatment with polaprezinc (150 mg/d) plus pantoprazole (40 mg/d) or treatment with rebamipide (300 mg/d) plus pantoprazole (40 mg/d). We evaluated the ulcer healing rate and condition of the ulcer at 4 weeks after dissection. The χ^2 or Fisher exact test and the Student *t* test were used.

Results: The ulcer healing rates at 4 weeks after dissection in the polaprezinc plus pantoprazole treatment group were not inferior compared with those in the rebamipide plus pantoprazole treatment group, both in the intention-to-treat analysis (90.3% and 91.4%, respectively, $P=0.523$) and per-protocol analysis (89.9% and 91.1%, respectively, $P=0.531$). The short procedure time was an independent predictive factor for a high ulcer healing rate (odds ratio: 0.975; 95% confidence interval: 0.958-0.993; $P=0.006$).

Conclusion: The polaprezinc plus PPI treatment showed non-inferiority to rebamipide plus PPI treatment in the ulcer healing rate at 4 weeks after ESD.

Key Words: polaprezinc, endoscopic submucosal dissection, ulcer

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Endoscopic submucosal dissection (ESD) is widely used to treat gastric neoplasms.[1] Although ESD shows higher en-bloc and curative resection rates than endoscopic mucosal resection, it causes larger and deeper artificial ulcers than endoscopic mucosal resection. A larger artificial ulcer is a risk factor of delayed bleeding.[2]

Therefore, the management of artificial ulcers is important. Proton pump inhibitors (PPIs), histamine-2 receptor antagonists, antacids, and mucosal protective drugs may heal artificial ulcers induced by ESD faster. However, there is no consensus with regard to optimal drugs and the proper duration. PPIs have been known to be the most effective type of drug for the treatment of artificial ulcers. However, in some studies, PPI monotherapy was not sufficient to heal ESD-induced artificial ulcers.[3]

Rebamipide is a mucoprotective agent that accelerates ulcer healing.[4] Rebamipide increases the glycoprotein content in gastric mucus and decreases reactive oxygen species.[5,6] Therefore, it protects the gastric mucosa and promotes quality of ulcer healing. Polaprezinc, a zinc-L-carnosine chelate compound, is used for the treatment of gastric ulcer. It exerts gastric mucosal protection and promotes ulcer healing through antioxidant activity.[7] There is a report that polaprezinc plus PPI treatment prevented protrusion of the ulcer base during the healing of ESD-induced artificial ulcers compared with PPI monotherapy.[8] In this study, we aimed to compare the rate of ulcer healing between polaprezinc and PPI combination therapy and rebamipide and PPI combination therapy.

METHODS

Patients

Between November 2014 and April 2016, we enrolled patients who underwent ESD for gastric neoplasms for this prospective, randomized, controlled study, which was conducted at the 2 hospitals of Yonsei University College of Medicine. Written informed consent was obtained from all patients before study enrollment. Inclusion criteria were (1) age 20 to 80 years and (2) patients pathologically diagnosed

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with gastric adenoma or cancer who were eligible for ESD. Exclusion criteria were (1) use of medication such as PPIs, histamine-2 receptor antagonists, or other mucosal protective drugs within 2 weeks before enrollment; (2) those who expected to take nonsteroidal anti-inflammatory drugs (including aspirin) and steroids within 2 weeks before enrollment; (3) history of upper gastrointestinal surgery; (4) history of allergy to a PPI, rebamipide, or polaprezinc; and (5) significant cardiovascular, renal, hepatic, neurotic, or psychological disorders.

The institutional review board of Severance and Gangnam Severance Hospitals approved this study. This study was registered with clinicaltrials.gov (identifier 02243618).

Study Design (Sample Size, Randomization, and Follow-up)

On the basis of a previous study,[9] the ulcer healing rate of the PPI and rebamipide arm after 4 weeks of administration was 95%, and the SD was 11%. The sample size was calculated by using an α error of 0.025, statistical power of 0.9, and 1-sided test. The calculated sample size was 103 lesions in each arm, for a total of 218 patients, allowing for a 5% dropout rate determined by assuming a noninferiority margin of 5% and standard deviation of 11%.

A single study coordinator performed the randomization process using a computer-generated randomization table. Patients were randomly assigned to one of 2 groups (PPI plus rebamipide or PPI plus polaprezinc). All patients received an intravenous injection of 40 mg of pantoprazole twice on the first 2 days after ESD. Beginning on the third day after ESD, the patients in the PPI plus rebamipide group took 40 mg of oral pantoprazole once a day and 100 mg rebamipide 3 times a day for 28 days; the patients in the PPI plus polaprezinc group took 40 mg of oral pantoprazole once a day and 75 mg of polaprezinc twice a day for 28 days.

The enrolled patients underwent follow-up endoscopy at 4 weeks after ESD to evaluate the degree of ulcer healing. The adverse events and compliance with taking the drugs were evaluated at 4 weeks. The patients who had low medication compliance (< 80%) and took the prohibited drugs mentioned in the exclusion criteria were excluded in the per-protocol analysis.

Evaluation of the Primary and Secondary Outcomes

The primary endpoint was the ulcer healing rate at 4 weeks, which was calculated as follows: [(initial ulcer area−ulcer area at 4 wk)×100/initial ulcer area]. The diameter of the ulcer was measured by using an endoscopic forcep (Olympus Optical Co. Ltd, Tokyo, Japan) (Supplementary Fig. 1, Supplemental Digital Content 1, http://links.lww.com/JCG/A558). Ulcer areas were calculated by multiplying these 2 diameters. The secondary endpoints were the proportion of patients based on the ulcer stage, which was scarring, and quality of ulcer healing at 4 weeks. The ulcer stage was assessed by using the classification of Sakita and Fukutomi,[10] and described as active (A1, A2), healing (H1, H2), and scarring (S1, S2) stages.

Statistical Analysis

The χ^2 test or Fisher exact test was used to compare categorical parameters. The Student *t* test was used to compare continuous variables. Risk factors affecting the ulcer healing rate were evaluated using logistic regression analysis. The accepted significance level was *P*-value < 0.05. All statistical analyses were performed using SPSS version 23.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS

Baseline Characteristics

Among 218 patients, 109 patients each were randomly allocated to the PPI plus rebamipide and PPI plus polaprezinc

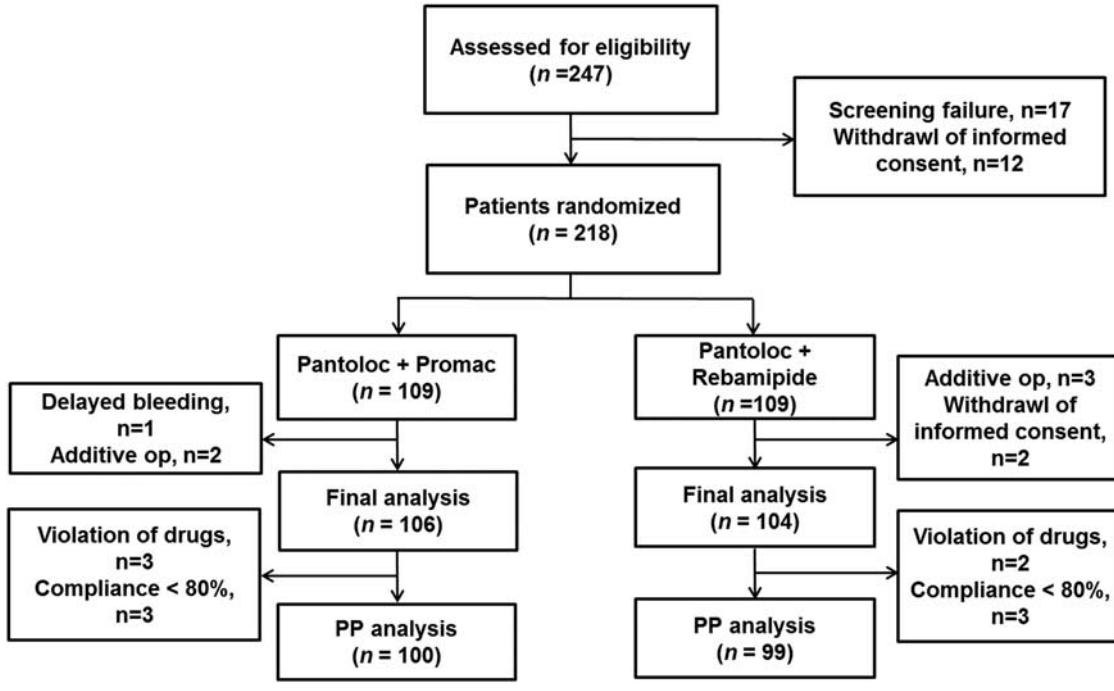

FIGURE 1. Flow chart of patients. PP indicates per-protocol.

group. Among them, 8 patients dropped out of the study because of delayed bleeding (1 patient in the PPI plus rebamipide group), additive surgery owing to a positive resection margin, or withdraw of informed consent. Thus, the 210 patients (106 in the PPI plus rebamipide group and 104 in the PPI plus polaprezinc group) who completed the study protocol were included in the full analysis. After excluding patients on the basis of study protocols such as <80% drug compliance or taking forbidden drugs, the data for 100 patients in the PPI plus rebamipide group and 99 patients in the PPI plus polaprezinc group were used in the per-protocol analysis (Fig. 1). There were no significant differences between the 2 groups in terms of age and sex, and histopathology, location, gross appearance, and diameter of the tumor and in terms of ulcer size, en-bloc resection rate, and procedure time. *Helicobacter pylori* infection developed significantly more in the PPI plus rebamipide group than in the PPI plus polaprezinc group (Table 1).

Healing Rates of Iatrogenic Ulcers at 4 Weeks After ESD

The average ulcer healing rate of all patients at 4 weeks after ESD was 90.5%. The ulcer healing rate was not significantly higher in the PPI plus rebamipide group than in the PPI plus polaprezinc group, both in the full analysis (91.4% and 90.3%, respectively; $P=0.523$) and per-protocol analysis (91.1% and 89.9%, respectively; $P=0.531$). The percentage of ulcers in the scarring stage at 4 weeks after ESD was not significantly higher in the PPI plus rebamipide group than in the PPI plus polaprezinc group, both in the full analysis (10.4% and 9.6%, respectively; $P=0.953$) and per-protocol analysis (9.0% and 7.1%, respectively; $P=0.846$) (Table 2).

TABLE 1. Baseline Characteristics of the Enrolled Patients

	n (%)		
Variables	**Polaprezinc Plus Pantoprazole (N = 104)**	**Rebamipide Plus Pantoprazole (N = 106)**	***P***
Age (mean ± SD) (y)	63.1 ± 8.8	63.1 ± 8.8	0.968
Sex			0.747
Male	78 (75.0)	82 (77.4)	
Female	26 (25.0)	24 (22.6)	
Histopathology			0.963
Adenoma	52 (50.0)	55 (51.9)	
Carcinoma	48 (46.2)	47 (44.3)	
Other	4 (3.8)	4 (3.8)	
Location			0.252
Upper stomach	52 (50.0)	64 (60.4)	
Middle stomach	39 (37.5)	34 (32.1)	
Lower stomach	13 (12.5)	8 (7.5)	
Gross tumor appearance			0.598
Elevated	66 (63.5)	65 (61.3)	
Flat	17 (16.3)	14 (13.2)	
Depressed	21 (20.2)	27 (25.5)	
Longest diameter of the tumor (mean ± SD) (mm)	13.8 ± 6.5	15.5 ± 7.1	0.076
Post-ESD ulcer size (mean ± SD) (mm^2)	865.2 ± 477.1	888.2 ± 422.8	0.712
Specimen size after fixation (mean ± SD) (mm^2)	876.2 ± 440.6	878.6 ± 430.2	0.968
En-bloc resection rate	102 (98.1)	105 (99.1)	0.620
Procedure time (mean ± SD) (min)	29.9 ± 29.7	26.5 ± 20.8	0.334
Smoker	27 (26.0)	25 (23.6)	0.750
Diabetes mellitus	9 (8.7)	17 (16.0)	0.142
Hypertension	41 (39.4)	47 (44.3)	0.487
Helicobacter pylori infection	35 (33.7)	51 (48.1)	0.036
Body mass index (mean ± SD) (kg/m^2)	24.6 ± 2.7	24.0 ± 2.9	0.153

ESD indicates endoscopic submucosal dissection.

Subgroup Analysis of the Iatrogenic Ulcer Healing Rates

We performed subgroup analysis to evaluate the risk factors that affect the ulcer healing rate. There were no significant predictive factors for a superior ulcer healing rate between the PPI plus rebamipide group and PPI plus polaprezinc group (Table 3). In addition, we assessed the independent factors for predicting an ulcer healing rate >90.5%, the mean average healing rate in this study, in multivariate analysis. The procedure time was an independent factor for a higher ulcer healing rate (Table 4).

DISCUSSION

In this study, the ulcer healing rates at 4 weeks after ESD in the polaprezinc plus PPI treatment group were not inferior compared with those in the rebamipide plus pantoprazole treatment group. There are many reports about the effect of rebamipide on the ulcer healing rate after ESD.[3,9,11,12] Those studies showed that PPI plus rebamipide is superior to PPI monotherapy for healing artificial ulcers after ESD. However, there are no reports about the effect of polaprezinc on the artificial ulcer healing rate after ESD compared with rebamipide. Polaprezinc, which is a complex chelating agent consisting of L-carnosine and zinc, is widely used as a mucoprotective agent to treat gastric ulcers.[13] The mechanisms of polaprezinc are independent of prostaglandin, and polaprezinc has anti-inflammatory and antioxidant effects.[14,15] The zinc L-carnosine ameliorates hydrochloric acid-induced mucosal injury by inducing heat shock protein (HSP)-72 expression.[16] The overexpression of HSP72 protects various organs and cells including gastric mucosal cells against stress conditions.[17,18] One study compared the effects of polaprezinc with those of rebamipide on gastric mucosal protection.[19] Polaprezinc showed gastric mucosal protection similar to rebamipide by reducing the levels of inflammatory cytokines and increasing the expression of antioxidant enzymes, growth factors, and HSP. In addition, polaprezinc is helpful for facilitating heal in various conditions, such as radiation, chemotherapy injury, liver fibrosis, and inflammatory bowel disease.[20] Polaprezinc was used to heal iatrogenic ulcers after ESD in only 1 study.[8] The PPI plus polaprezinc group showed significantly better ulcer healing and more prevention of protrusion of the ulcer base, indicating that this group had a higher quality of ulcer healing than the PPI monotherapy group.

In this study, the PPI plus polaprezinc group showed noninferiority in ulcer healing compared with the PPI plus rebamipide group. In addition, the only predictor for a higher than average ulcer healing rate was the short procedure time. The long procedure time was an independent risk factor for a low ulcer healing rate, and this result might be associated with the use of more electrocautery during ESD. Electrocautery has been known to result in proper muscle damage.[21] Therefore, electrocautery caused delayed ulcer healing after ESD.[22] In addition, the patients in the PPI plus rebamipide group took 100 mg rebamipide 3 times a day

TABLE 2. Ulcer Healing Rates at 4 Weeks After ESD

	Intent-to-treat Analysis			Per-protocol Analysis		
Variables	**Polaprezinc+PPI (n = 104)**	**Rebamipide+PPI (n = 106)**	***P***	**Polaprezinc+PPI (n = 99)**	**Rebamipide+PPI (n = 100)**	***P***
Longest diameter of the ulcer (mm)						
Initial	35.5 ± 9.4	36.0 ± 8.8	0.668	35.5 ± 9.6	35.7 ± 8.7	0.838
4 wk after ESD	11.8 ± 8.1	12.0 ± 8.2	0.917	12.0 ± 8.1	12.1 ± 8.3	0.892
Area of the ulcer (mm^2)						
Initial	865.2 ± 477.1	888.2 ± 422.8	0.712	866.0 ± 488.5	871.9 ± 415.7	0.926
4 wk after ESD	96.6 ± 155.4	93.4 ± 140.9	0.881	99.9 ± 159.4	97.2 ± 145.8	0.904
Healing rate at 4 wk (%)	90.3	91.4	0.523	89.9	91.1	0.531
Scar stages at 4 wk	10 (9.6)	11 (10.4)	0.953	7 (7.1)	9 (9.0)	0.846

ESD indicates endoscopic submucosal dissection; PPI, proton pump inhibitor.

and the patients in the PPI plus polaprezinc group took 75 mg of polaprezinc twice a day. Therefore, one advantage of polaprezinc compared with rebamipide is its twice a day dosing. However, the cost of polaprezinc was 216 Korean won (KRW) and rebamipide 99 KRW, respectively. Therefore, the daily cost of polaprezinc was 432 KRW and rebamipide 297 KRW. The cost of polaprezinc was higher than that of rebamipide.

There is no fundamental guideline to determine the appropriate PPI dose and treatment duration for iatrogenic ulcer healing. Some studies reported variable treatment duration (1, 2, 4, and 8 wk) and PPI dose (half or full dose) for ESD ulcers.[23–26] The predictors for delayed ulcer healing have been known to be the tumor location, comorbidity, larger tumor size, and electrocoagulation.[22,27] In this study, the patients took oral PPI plus rebamipide or polaprezinc for 4 weeks. The average ulcer healing rate was 90.5%. This result was comparable with that of previous studies.[9,19] However, the proportion of patients with scarring stage was low (16/199, 8.0%). Therefore, we could not evaluate the quality of ulcer healing well. Shin et al[9] reported that the scarring stage rate at 4 weeks was 20.8% (53/255) after ESD in both the PPI and rebamipide and PPI monotherapy groups. Furthermore, Nakamura et al[12] showed that the scarring stage rate at 4 weeks was 14.4% (15/104) after ESD in both the PPI and rebamipide and PPI monotherapy groups. Although the scarring stage rate at 4

TABLE 3. Predictors of Higher Ulcer Healing Rate at 4 Weeks After ESD in Univariate Analysis

	Intent-to-treat Analysis [n (%)]			Per-protocol Analysis [n (%)]		
Variables	**Polaprezinc+PPI (n = 104)**	**Rebamipide+PPI (n = 106)**	***P***	**Polaprezinc+PPI (n = 99)**	**Rebamipide+PPI (n = 100)**	***P***
Initial longest diameter of the ulcer (mm)						
< 35	49 (91.4)	48 (92.6)	0.575	47 (91.1)	46 (92.4)	0.579
≥ 35	55 (88.2)	58 (90.0)	0.501	52 (87.7)	54 (89.5)	0.512
Initial area of the ulcer (mm^3)						
< 800	51 (90.2)	54 (92.4)	0.316	49 (90.0)	52 (92.2)	0.313
≥ 800	53 (89.2)	52 (89.9)	0.803	50 (88.7)	48 (89.3)	0.830
Procedure time (min)						
< 21	46 (93.5)	57 (92.1)	0.540	43 (93.2)	54 (91.8)	0.566
≥ 21	58 (86.7)	49 (90.1)	0.196	56 (86.4)	46 (89.6)	0.239
Age (y)						
< 64	47 (90.3)	56 (90.4)	0.962	46 (90.1)	53 (90.0)	0.948
≥ 64	57 (89.2)	50 (92.1)	0.286	53 (88.6)	47 (91.8)	0.257
Pathology						
Adenoma	52 (91.0)	55 (92.1)	0.609	48 (90.4)	53 (91.9)	0.515
Carcinoma	48 (89.3)	47 (89.6)	0.900	47 (89.1)	43 (89.0)	0.955
Other	4 (78.3)	4 (96.9)	0.192	4 (78.3)	4 (96.9)	0.192
Location						
Antrum	52 (89.5)	64 (92.3)	0.235	49 (89.0)	59 (91.8)	0.243
Other	52 (89.9)	42 (89.5)	0.880	50 (89.6)	41 (89.4)	0.939
Helicobacter pylori infection						
No	69 (89.1)	55 (90.6)	0.546	64 (88.4)	52 (90.2)	0.490
Yes	35 (91.0)	51 (91.8)	0.720	35 (91.0)	48 (91.5)	0.840
Combined diseases						
No	56 (88.2)	50 (90.6)	0.377	54 (87.8)	48 (90.3)	0.376
Yes	48 (91.5)	56 (91.7)	0.920	45 (91.1)	52 (91.3)	0.927

ESD indicates endoscopic submucosal dissection; PPI, proton pump inhibitor.

TABLE 4. Independent Predictors for Higher Than Average Ulcer Healing Rates (≥90.5%) at 4 Weeks After ESD in Logistic Regression Analysis

	Univariate Analysis			Multivariate Analysis	
Variables	**Ulcer Healing Rate <90.5%**	**Ulcer Healing Rate ≥90.5%**	***P***	**Odds Ratio (95% CI)**	***P***
Age (y)	61.5 ± 7.6	63.7 ± 9.1	0.097	1.039 (0.999-1.080)	0.056
Underlying diseases	28/59 (47.5)	76/151 (50.3)	0.760	0.704 (0.353-1.404)	0.318
Ulcer location (antrum)	29/59 (49.2)	83/151 (55.0)	0.538	0.824 (0.410-1.655)	0.586
Initial longest diameter of the ulcer	37.9 ± 10.2	34.9 ± 8.5	0.054	0.972 (0.874-1.080)	0.593
Initial area of the ulcer	962.4 ± 463.7	843.4 ± 441.0	0.085	1.000 (0.998-1.003)	0.649
Carcinoma	29/59 (49.2)	66/151 (43.7)	0.538	0.801 (0.413-1.553)	0.511
Helicobacter pylori infection	25/59 (42.4)	61/151 (40.4)	0.876	1.079 (0.549-2.120)	0.825
Procedure time	38.8 ± 36.5	24.1 ± 18.3	0.004	0.975 (0.958-0.993)	0.006
PPI+polaprezinc	25/59 (42.4)	81/151 (53.6)	0.168	0.648 (0.340-1.233)	0.186

CI indicates confidence interval; ESD, endoscopic submucosal dissection; PPI, proton pump inhibitor.

weeks herein was lower than that in other studies, the incidence of bleeding was low (1/210, 0.4%). This low bleeding rate might be due to complete electrocoagulation of exposed vessels of the iatrogenic ulcer.

In a previous study, polaprezinc showed better ulcer healing and prevention of protrusion of the ulcer base after ESD.[8] In this study, we did not evaluate the effects of quality of ulcer healing after ESD in the polaprezinc plus PPI group because the proportion of patients with ulcer scarring stage was low. Further studies will be needed to investigate the effects of polaprezinc on the quality of ulcer healing.

In conclusion, polaprezinc plus PPI treatment showed noninferiority to rebamipide plus PPI treatment in the 4-week ESD-induced ulcer healing rate.

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