A Multicenter, Randomized, Controlled Trial of Rebamipide Plus Lansoprazole for the Treatment of Postendoscopic Submucosal Dissection Ulcers

Bin Yan, MD[1], Zhongsheng Lu, MD[1], Zhizheng Ge, MD[2], Side Liu, MD[3], Xuegang Guo, MD[4], Dean Tian, MD[5], Yuxiu Yang, MD[6], Xiaobo Li, MD[2], Wei Gong, MD[3], Zhiguo Liu, MD[4], Mei Liu, MD[5], Bingxi Zhou, MD[6], Kabing Zhao, MD[1], Fei Pan, MD[1], Jing Yang, MD[1] and Yunsheng Yang, MD[1]

OBJECTIVES: **To evaluate the healing efficacy of rebamipide and lansoprazole combination therapy with lansoprazole alone for endoscopic submucosal dissection (ESD)–induced ulcers and clarify the ulcer healing-associated factors.**

METHODS: **Three hundred patients were randomized into control and experimental groups after they underwent ESD. The patients received intravenous pantoprazole (30 mg) every 12 hours and oral rebamipide (100 mg, experimental group) or placebo (control group) 3 times daily on days 1–3. On days 4–56, patients received oral lansoprazole (30 mg daily) and rebamipide (100 mg) or placebo 3 times daily. Endoscopic evaluations were performed at postoperative weeks 4 and 8.**

RESULTS: **At week 4, the ulcer reduction rate was significantly higher in the experimental than in the control group (0.97 ± 0.034 vs. 0.94 ± 0.078; $P < 0.001$). The ulcer healing (18.2% vs 20.3%; $P = 0.669$) and ulcer improvement rates (94.2% vs 88.7%; $P = 0.109$) in the 2 groups were not significantly different. At week 8, the ulcer healing and ulcer improvement rates were 90.6% and 100%, respectively, in both groups. Multivariate analysis showed that the combination treatment was an independent factor associated with ulcer area reduction after ESD. The maximum diameter of the initial ulcer (≥35.5 mm vs <35.5 mm) was an independent factor associated with the ulcer improvement rate after ESD.**

CONCLUSIONS: **The rebamipide and lansoprazole combination therapy can help accelerate the reduction rate of post-ESD ulcer compared with the lansoprazole monotherapy at 4 weeks of therapy.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A4

Clinical and Translational Gastroenterology 2019;10:e-00008. https://doi.org/10.14309/ctg.0000000000000008

INTRODUCTION

Endoscopic submucosal dissection (ESD), developed in Japan in the 1990s, is currently a widely accepted treatment for early gastric mucosal lesions because it is minimally invasive and enables the *en bloc* resection of mucosal lesions (3). Because of the widespread use of endoscopy and the higher rate of early lesion detection, the application of ESD has become increasingly common. This trend has been accompanied by the increasing concern about ESD complications. These procedures sometimes lead to deep and large gastrointestinal ulcers, resulting in an increased risk of perforation, bleeding, and abdominal pain. The management of large ulcers induced by ESD is a challenge and, hence, has become a focus of clinical research.

Currently, there is no standardized regimen for the treatment of gastric large ulcers induced by ESD, but proton pump inhibitors (PPIs) are still commonly used for 8 weeks for this purpose. Nevertheless, rebamipide has been evaluated for the treatment of post-ESD ulcers, and its clinical efficacy has been verified by numerous investigators (8). Effective treatment regimens for post-ESD ulcers might involve rebamipide alone or in combination with PPIs. Some studies have indicated that the clinical efficacy of rebamipide alone is similar, or even superior, to that of PPIs alone (9). Others have shown that rebamipide combined

[1]Department of Gastroenterology and Hepatology, Chinese PLA General Hospital, Beijing, China; [2]Department of Gastroenterology and Hepatology, Renji Hospital, Shanghai, China; [3]Department of Gastroenterology and Hepatology, Nanfang Hospital, Guangzhou, Guangdong Province, China; [4]Department of Gastroenterology and Hepatology, Xijing Hospital, Xian, Shanxi province, China; [5]Department of Gastroenterology and Hepatology, Tongji Hospital, Wuhan, Hubei province, China; [6]Department of Gastroenterology and Hepatology, Henan provincial People's Hospital, Zhengzhou, Henan province, China. **Correspondence:** Yunsheng Yang, MD. E-mail: sunny301ddc@126.com.

Received June 4, 2018; accepted December 14, 2018; published online January 25, 2019

with PPIs can accelerate the healing of ulcers compared to monotherapy using PPIs (10–12). Given this, the present study was to determine whether PPIs combined with rebamipide would promote post-ESD ulcer healing more effectively than PPIs alone and explore the ulcer healing-associated factors.

METHODS

Experimental design

We performed a multicenter, prospective, randomized, double-blind, parallel-group, positive-controlled trial at 6 participating medical institutions (all AAA hospitals). The study was approved by the Ethical Review Committee of the Chinese PLA General Hospital and entered in the Chinese Clinical Trial Registry (registration number, ChiCTR-TRC-13003032). Each center recruited 50 patients (300 patients in total) admitted between May 2013 and December 2014. Patients were recruited if they had one of the following indications for ESD: (i) a gastric adenoma with low-grade to high-grade intraepithelial neoplasia (LIN and HIN, respectively) that was difficult to remove using conventional methods (e.g., endoscopic mucosal resection); (ii) a well-differentiated or moderately differentiated intramucosal carcinoma; (iii) a well-differentiated or moderately differentiated superficial gastric carcinoma without ulceration or with ulcers (the diameter <3 cm); (iv) an undifferentiated carcinoma <2 cm, without ulceration. All diagnoses were confirmed by gastroscopy and histopathology. Additional inclusion criteria included (i) age 18–80 years, (ii) absence of major cardiopulmonary disease and no history of hepatobiliary or other gastrointestinal disease or surgery, (iii) normal blood coagulation, and (iv) no use of antacids or mucosal protective agents within 2 weeks before enrollment. We excluded patients (i) who required additional antiulcer medications after enrollment; (ii) a well-differentiated or moderately differentiated superficial gastric carcinoma (invasion depth $\geq$500 μm) which further needs additional surgical treatment; (iii) who were pregnant, breastfeeding, or might become pregnant during the trial period; (iv) with severe intraoperative complications; (v) patients who needed antiplatelet medications. All patients voluntarily participated in the study and signed informed consent.

ESD operation procedures

Enrolled patients (n = 300) underwent endoscopic examinations and ESD procedures performed by experts with much experience in ESD. ESD knives and electrocautery settings are DualKnife (KD-650L; Olympus, Tokyo, Japan), ITknife2 (KD-611L; Olympus), Coagrasper (FD-410LR; Olympus), and Gastroscope (GIF-Q260J; Olympus). The margin of resection was marked using electrocoagulation and included approximately 0.5 cm of normal mucosal tissue around the lesion. We injected normal saline into the submucosa to lift the lesion and separate the submucosa from the muscular layer. The mucosa and submucosa on the outer edge of the lesion were incised along the previously

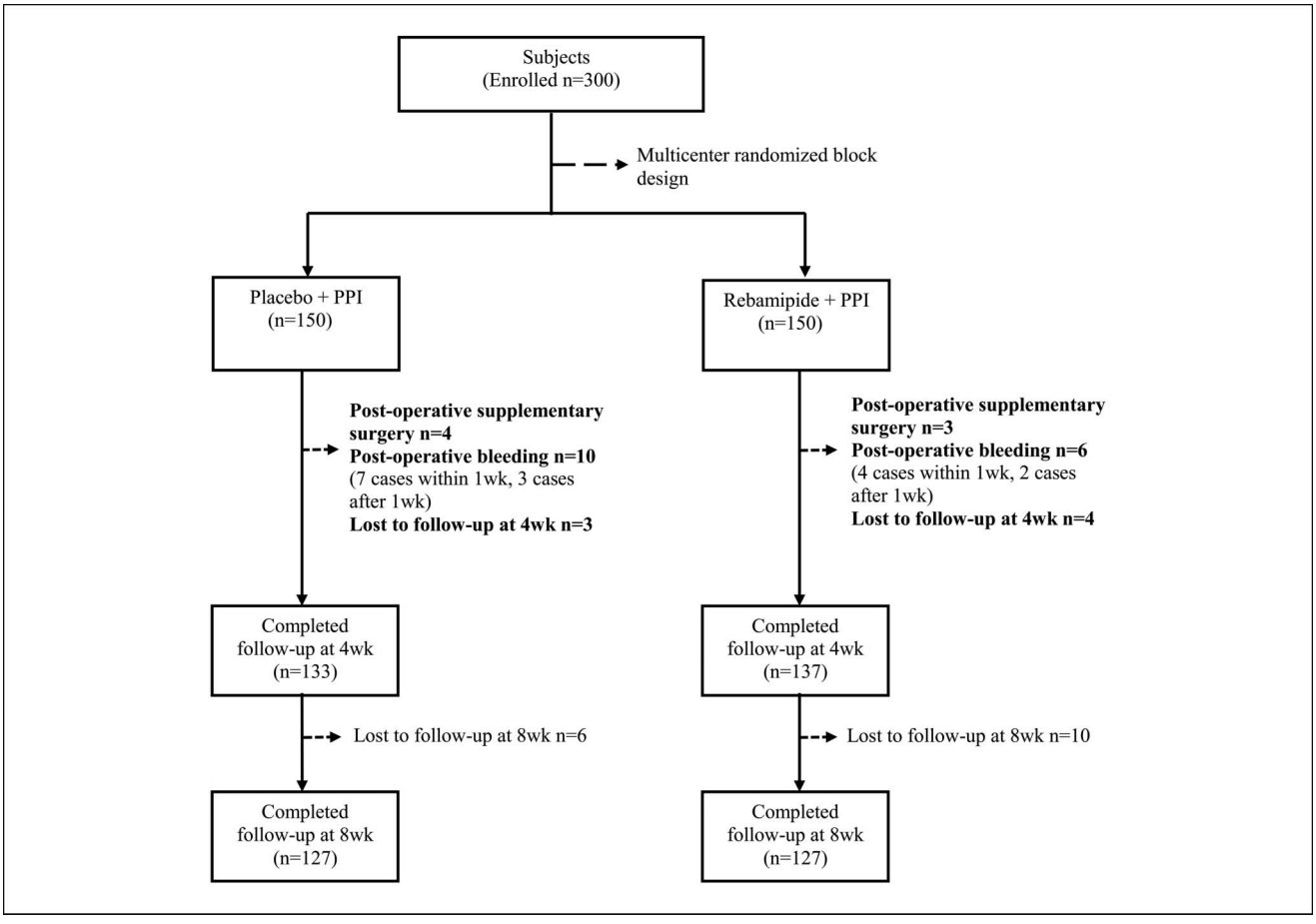

Figure 1. Flow chart of research procedure through the clinical trial. PPI, proton pump inhibitor.

Table 1. Characteristics of subjects and lesions

Characteristics	Control group, n = 150	Experimental group, n = 150	*P*-value
Gender (male/female)	106/44	103/47	0.706
Age (mean ± SD)	59.95 ± 10.10	59.80 ± 10.09	0.900
BMI (mean ± SD)	23.26 ± 2.94	23.24 ± 3.18	0.954
Pathological grade, n (%)			0.567
Cancer	9 (6.0)	14 (9.3)	
HIN	81 (54.0)	75 (50.0)	
LIN	36 (24)	32 (21.3)	
Others	24 (16.0)	29 (19.3)	
Lesion site, n (%)			0.944
Gastric antrum	77(51.3)	80(53.3)	
Angular incisure	27(18.0)	28(18.7)	
Distal gastric body	10(6.7)	11(7.3)	
Proximal gastric body	10(6.7)	6(4.0)	
Gastric fundus	6(4.0)	5(3.3)	
Gastric cardia	20(13.3)	20(13.3)	
Underlying disease (yes/No)	69/81	70/80	0.908
HP infection (yes/No)	31/59	26/63	0.453
Initial maximum diameter (mm)	35.05 ± 12.82	36.13 ± 13.63	0.483
Perpendicular line of maximum diameter (mm)	26.82 ± 10.57	27.77 ± 10.87	0.442
Ulcer area (mm^2)	1,058.79 ± 834.47	1,127.04 ± 851.57	0.452
Postoperative bleeding, n	10	6	0.304

BMI, body mass index; HIN, high-grade intraepithelial neoplasia; HP, *Helicobacter pylori*; LIN, low-grade intraepithelial neoplasia.

marked margin. Then, the submucosa was dissected until the mucosal lesion had been completely resected. Electrocoagulation was applied to exposed blood vessels in the post-ESD resection defects. The resected specimen was sent for pathologic examination. The measurements of the resected lesion and mucosal defects were recorded.

Patient grouping and drug administration

Enrolled patients were randomized into the experimental group (n = 150) or the control group (n = 150) by Statistical software. Patients in the control group received intravenous pantoprazole (30 mg every 12 hours; Nycomed Pharmaceutical Consultancy, Shanghai, China) and a placebo (3 times daily) on postoperative days 1–3. On postoperative days 4–56, they received oral lansoprazole (disintegrating tablets, 30 mg daily; Tianjin Takeda Pharmaceutical, Tianjin, China) and placebo (3 times daily). Patients in the experimental group received intravenous pantoprazole (30 mg every 12 hours) and oral rebamipide (100 mg 3 times daily; Zhejiang Yuan Li Jian Pharmaceutical, Hangzhou, China) on postoperative days 1–3. On postoperative days 4–56, they received oral lansoprazole (disintegrating tablets, 30 mg daily) and rebamipide (100 mg 3 times daily). Concurrent use of the following drugs was prohibited during the trial period: other PPIs, H_2-receptor antagonists (H2RA), and gastric mucosal protective agents, as well as nonsteroidal anti-inflammatory drugs, anticoagulants, and antiplatelet drugs.

Specimen measurement and surgical site evaluations

Endoscopic measurement of ulcer size. The resected specimen was spread out *in vitro* and fixed in place using pins. Calipers were used to directly measure the maximum diameter and the perpendicular line of the maximum diameter.

Endoscopic follow-up evaluations. Enrolled patients underwent follow-up endoscopy at 4 and 8 weeks postoperatively to evaluate ulcer healing. Four weeks postoperatively, a 5 mm diameter white paper disk (produced using a hole puncher) was positioned at the edge of the ulcer site using biopsy forceps placed through the endoscope biopsy channel. The ulcers were photographed using the paper disk as a reference. The photographic images were uploaded to a computer and measured using the Amedicom software system. The maximum diameter and perpendicular line of the maximum diameter were recorded (Supplementary Figure 1, Supplemental Digital Content, http://links.lww.com/CTG/A4).

Ulcer size and rate of reduction. The ulcer size and rate of reduction were calculated as follows: Ulcer area = ulcer maximum diameter × perpendicular line of maximum diameter (mm^2). Ulcer reduction rate at 4 weeks = (initial ulcer area − ulcer area at 4 weeks) × 100%/initial ulcer area. Ulcer reduction rate at 8 weeks = (initial ulcer area − ulcer area at 8 weeks) × 100%/initial ulcer area.

Endoscopic ulcer classification and healing evaluation. We staged each ulcer according to the classification system developed

by Sakita (13). Based on the endoscopic presentations, the ulcers were classified into 6 stages: active (A1 and A2), healing (H1 and H2), and scarring (S1 and S2). We classified treatment as effective (H-stage ulcers with ≥50% reduction in maximum diameter and S-stage ulcers) or not effective (H-stage ulcers with <50% reduction in maximum diameter and A-stage ulcers). The ulcer healing rate was calculated as the number of S-stage ulcers/total number of cases × 100%. The ulcer improvement rate was calculated as the number of effective cases/total number of cases × 100%. A team of 5 endoscopic experts blinded to patient groups performed the endoscopic staging of ulcer healing. The healing stages were assigned based on the consensus of 3 or more evaluators.

Statistical analysis

Independent third parties were responsible for performing the statistical analyses, participating in the experimental design and implementation, conducting sample blinding, managing the data, and completing the summary statistical report. SPSS for Windows, Version 13.0 (SPSS, Chicago, IL), was used for our statistical analyses. Quantitative variables were analyzed using the Wilcoxon signed-rank or Student's *t* test and are reported as mean ± s.d. Categorical variables were analyzed using the Pearson chi-squared test and are reported as the number of cases and percentages. All statistical analyses were 2-tailed tests and a *P* value <0.05 was considered statistically significant. Logistic regression analyses were performed to analyze factors influencing post-ESD ulcer reduction, ulcer healing, and ulcer improvement, respectively.

RESULTS

Characteristics of research subjects

Among the 300 subjects, 318 lesions were removed by ESD (due to statistical requirements, if a patient had multiple resected lesions, the healing of only one was assessed). We evaluated 133 control group patients at the 4-week follow-up. Four control cases were excluded because they required additional surgery to treat residual marginal disease, 10 were excluded because of bleeding that required repeat endoscopic treatment, and 3 cases were lost to follow-up. We assessed 137 experimental group patients at the 4-week follow-up. Three cases were excluded because they required additional surgery, 6 were excluded because of bleeding that required repeat endoscopic treatment, and 4 were lost to follow-up. In each group (experimental and control), 127 patients completed 8 weeks of treatment observation (6 control group and 10 experimental group cases were lost to follow-up). Details of the experimental procedure are shown in Figure 1. The characteristics of the research subjects in both groups were shown in Table 1. Our analysis demonstrated no statistically significant differences in the gender, age, body mass index (BMI), comorbidities, presence of *Helicobacter pylori* (Hp) infection, lesion pathological features or anatomical location, initial size of the post-ESD ulcer, or maximum or perpendicular diameter of the ulcer between the groups.

Outcomes of ulcer healing after combination therapy and monotherapy

The primary outcomes of ulcer healing after combination therapy and monotherapy were the ulcer reduction rates at 4 weeks of treatment. As shown in Table 2, the ulcer reduction rate was significantly higher in the experimental group than that in the control group after 4 weeks of treatment (97% vs 94%, $P < 0.001$). The secondary outcomes were the healing rate, the improvement rate, ulcer area, maximum diameter, and perpendicular diameter after 4 weeks of treatment or 8 weeks of treatment, which were also summarized in Table 2. After 4 weeks of treatment, the experimental group showed a post-ESD ulcer healing rate of 18.2% and an improvement rate of 94.2% whereas the control group showed a post-ESD ulcer healing rate of 20.3% and an improvement rate of 88.7%. The healing rate and improvement rate of post-ESD ulcers did not show statistically significant differences between the 2 drug regimens ($P > 0.05$). Moreover, at 4 weeks of treatment, the differences between the experimental group and control group in terms of ulcer area (36.35 ± 51.36 mm^2 vs 55.04 ± 67.56 mm^2), maximum diameter (6.30 ± 5.04 mm vs

Table 2. Healing of ulcer postendoscopic submucosal dissection in the experimental and control groups

Factors	Control group, n = 133	Experimental group, n = 137	*P*-value
Ulcer maximum diameter, mm			
Initial	34.57 ± 12.43	36.40 ± 13.60	0.250
4 wk postoperatively	7.80 ± 5.96	6.30 ± 5.04	0.027[a]
Perpendicular line of maximum diameter, mm			
Initial	26.68 ± 10.68	27.88 ± 10.61	0.353
4 wk postoperatively	4.75 ± 3.64	3.55 ± 3.18	0.004[a]
Ulcer area, mm^2			
Initial	1,033.52 ± 840.04	1,133.90 ± 832.61	0.325
4 wk postoperatively	55.04 ± 67.56	36.35 ± 51.36	0.011[a]
Ulcer reduction rate at 4 wk, %	0.94 ± 0.078	0.97 ± 0.034	<0.001[a]
Ulcer healing rate at 4 wk, %	27/133 (20.3%)	25/137 (18.2%)	0.669
Ulcer improvement rate at 4 wk, %	118/133 (88.7%)	129/137 (94.2%)	0.109
Ulcer reduction rate at 8 wk, %	115/127 (90.6%)	115/127 (90.6%)	1

[a] $P < 0.05$, difference was statistically significant.

7.80 ± 5.96 mm), and perpendicular diameter (3.55 ± 3.18 mm vs 4.74 ± 3.64 mm) were statistically significant ($P = 0.011$, $P = 0.027$, $P = 0.004$, respectively). At 8 weeks, the ulcer healing rate in both groups was 90.6%, and the ulcer improvement rate in both groups was 100% (Table 2).

Subgroup analysis of factors influencing ulcer reduction post-ESD

Subgroup analysis was performed to investigate the factors affecting the efficacy of rebamipide plus lansoprazole for post-ESD ulcer reduction at 4 weeks (Table 3). For factors recorded as numerical data, the group's mean value was used to determine thresholds for age (60 years), BMI (23.22), initial ulcer area (1,084.45 mm^2), initial maximum diameter (35.50 mm), and initial perpendicular diameter (27.29 mm) that defined 2 factor-based subgroups. For qualitative factors, patients were divided into subgroups based on existing categories or the presence or absence of the factor. The results indicated that the subgroup factors related to ulcer healing included patient age and BMI; initial ulcer area, maximum diameter, and perpendicular diameter; lesion site and pathological grade; and the presence of underlying disease or Hp infection.

Table 3. Subgroup analysis of ulcer reduction postendoscopic submucosal dissection in the experimental and control groups

Factors	Control group, n = 133 (average reduction rate)	Experimental group, n = 137 (average reduction rate)	*P*-value
Initial maximum diameter, mm			
<35.50	79 (93.4)	79 (97.6)	<0.001[a]
≥35.50	54 (94.7)	58 (96.3)	0.065
Initial perpendicular line of maximum diameter, mm			
<27.29	75 (92.6)	76 (97.3)	<0.001[a]
≥27.29	58 (95.6)	61 (96.7)	0.116
Initial ulcer area, mm^2			
<1,084.45	86 (93.1)	85 (97.6)	<0.001[a]
≥1,084.45	47 (95.5)	52 (96.2)	0.373
Age, yr			
<60	66 (93.4)	64 (97.4)	0.003[a]
≥60	67 (94.4)	73 (96.8)	0.001[a]
BMI			
<23.22	65 (94.4)	83 (97.4)	0.007[a]
≥23.22	68 (93.5)	54 (96.5)	0.003[a]
Lesion site			
Gastric antrum	66 (94.3)	72 (97.6)	0.002[a]
Others	67 (93.5)	65 (96.4)	0.008[a]
Pathological grade			
Cancer + HIN	56 (93.5)	55 (97.8)	0.001[a]
LIN + others	77 (94.2)	82 (96.5)	0.008[a]
Underlying disease			
No	60 (93.1)	64 (97.6)	<0.001[a]
Yes	73 (94.6)	73 (96.6)	0.029[a]
HP infection	n = 81	n = 85	
No	54 (93.1)	61 (96.8)	0.007[a]
Yes	27 (92.2)	24 (97.5)	0.003[a]

BMI, body mass index; HIN, high-grade intraepithelial neoplasia; *Helicobacter pylori*; LIN, low-grade intraepithelial neoplasia.
[a]$P < 0.05$, difference was statistically significant.

Logistic regression analysis of factors influencing post-ESD ulcer reduction

Univariate and multivariate logistic regression models were used to analyze the factors influencing ulcer reduction at 4 weeks. The results are shown in Table 4. The dependent variable was a post-ESD ulcer reduction. Moreover, the mean ulcer reduction rate defines the cutoff value of the variable (≥95% vs <95%). The independent variables were the relevant variables determined by our subgroup analysis. Univariate analysis revealed that lesion site (gastric antrum vs others), patient sex, and the use of combination therapy (PPI + rebamipide vs PPI monotherapy) were associated with ulcer reduction. Multivariate analysis indicated that combination therapy (PPI + rebamipide vs PPI monotherapy) and lesion site (gastric antrum vs others) were independent factors associated with greater post-ESD ulcer reduction. The adjusted odds ratios (ORs) were 4.31 (2.51–7.39) and 0.47 (0.28–0.80), respectively.

Logistic regression analysis of factors influencing post-ESD ulcer healing

Univariate and multivariate logistic regression models were used to analyze the factors affecting post-ESD ulcer healing at 4 weeks. The results are shown in Table 5. The dependent variable was post-ESD ulcer healing. The independent variables were the relevant variables determined by our subgroup analysis. Our univariate analysis revealed that pathological grade (cancer + HIN vs LIN + others), initial ulcer area (≥1,084.45 mm^2 vs <1,084.45 mm^2), initial maximum diameter (≥35.5 mm vs <35.5 mm), and perpendicular diameter (≥27.29 mm vs <27.29 mm) were related to ulcer healing. The multivariate analysis indicated that pathological grade (cancer + HIN vs LIN + others) and initial maximum diameter (≥35.5 mm vs <35.5 mm) were independent factors that influenced post-ESD ulcer reduction. The adjusted ORs were 0.33 (0.17–0.62) and 0.36 (0.17–0.75), respectively.

Logistic regression analysis of factors influencing post-ESD ulcer improvement

Univariate and multivariate logistic regression models were used to analyze the factors that affect post-ESD ulcer improvement at 4 weeks. The results are shown in Table 6. The dependent variable was whether the post-ESD ulcer improved. The independent variables were the relevant variables determined by our subgroup analysis. Univariate analysis revealed that the initial ulcer area (≥1,084.45 mm^2 vs <1,084.45 mm^2), initial maximum diameter (≥35.5 mm vs <35.5 mm), and perpendicular diameter (≥27.29 mm vs <27.29 mm) were related to ulcer improvement. Multivariate analysis indicated the initial maximum diameter (≥35.5 vs <35.5) was an independent factor that influenced post-ESD ulcer reduction. The adjusted OR was 0.34 (0.14–0.81, $P = 0.015$).

Table 4. Logistic regression analysis of factors influencing ulcer reduction postendoscopic submucosal dissection

Factors	Univariate analysis (n = 270)					Multivariate analysis (n = 270)		
	Ulcer reduction rate <95.5%	Ulcer reduction rate ≥95.5%	*P*-value	OR	95% CI	*P*-value	OR	95% CI
Age, ≥60/<60	58/44	82/86	0.199	0.72	0.44–1.19			
BMI, ≥23.25/<23.25	56/46	66/102	0.012	0.53	0.32–0.88			
HP infection, yes/no	25/45	26/70	0.234	0.67	0.34–1.30			
Lesion site, gastric antrum/others	61/41	71/97	0.005[a]	0.49	0.30–0.81	0.006[a]	0.47	0.28–0.80
Pathological grade, cancer + HIN/LIN + others	67/35	92/76	0.077	0.63	0.38–1.05			
Initial maximum diameter, ≥35.5/<35.5	48/54	64/104	0.147	0.69	0.42–1.14			
Initial perpendicular line of maximum diameter, ≥27.29/<27.29	43/59	76/92	0.621	1.13	0.69–1.86			
Initial ulcer area, ≥1,084.45/<1,084.45	42/60	57/111	0.231	0.73	0.44–1.22			
Underlying disease, yes/no	56/46	90/78	0.832	0.95	0.58–1.55			
Gender, male/female	78/24	109/59	0.045[a]	1.76	1.01–3.07			
(PPI + rebamipide)/PPI	30/72	107/61	<0.001[a]	4.21	2.48–7.15	<0.001[a]	4.31	2.51–7.39

n = 270 (excluding 30 patients lost to follow-up).
CI, confidence interval; HIN, high-grade intraepithelial neoplasia; HP, *Helicobacter pylori*; LIN, low-grade intraepithelial neoplasia; OR, odds ratio; PPI, proton pump inhibitor.
[a]$P < 0.05$, difference was statistically significant.

DISCUSSION

The PPI treatment of 8 weeks is the standard therapy for the common gastric ulcer. However, there is no standardized regimen for the treatment of gastric large iatrogenic ulcers induced by ESD. Previous medical therapy contained the PPI alone, mucosa protectant alone, as well as the combination of these 2 drugs, and the course for the treatment is 4 to 8 weeks. Previous studies showed that with PPI alone or mucosa protectant alone for 4 weeks, the ulcer healing rate was 11.5%–36%; however, the ulcer healing rate in the combination therapy group was 9.5%–68%, indicating that the combination therapy was better. In our study, we performed a large-scale, multicenter, prospective, randomized, double-blind, parallel-group, positive-controlled trial to evaluate optimal treatment for post-ESD ulcer.

Table 5. Logistic regression analysis of factors influencing ulcer healing postendoscopic submucosal dissection

Factors	Univariate analysis (n = 270)					Multivariate analysis (n = 270)		
	Ulcer not healed	Ulcer healed	*P*-value	OR	95% CI	*P*-value	OR	95% CI
Age, ≥60/<60	119/99	21/31	0.066	0.56	0.31–1.04			
BMI, ≥23.25/<23.25	100/118	22/30	0.643	0.87	0.47–1.60			
HP infection, yes/no	46.95	5/20	0.207	0.52	0.18–1.46			
Lesion site, gastric antrum/others	111/107	21/31	0.172	0.65	0.35–1.21			
Pathological grade, cancer + HIN/LIN + others	141/77	18/34	<0.001[a]	0.29	0.15–0.55	0.001[a]	0.33	0.17–0.62
Initial maximum diameter, ≥35.5/<35.5	101/117	11/41	0.001[a]	0.31	0.15–0.64	0.006[a]	0.36	0.17–0.75
Initial perpendicular line of maximum diameter, ≥27.29/<27.29	10/115	16/36	0.032[a]	0.50	0.26–0.95			
Initial ulcer area, ≥1,084.45/<1,084.45	88/130	11/41	0.010[a]	0.40	0.19–0.81			
Underlying disease, yes/no	113/105	33/19	0.131	1.61	0.87–3.01			
Gender, male/female	156/62	31/21	0.093	1.70	0.91–3.19			
(PPI + rebamipide)/PPI	112/106	25/27	0.669	0.88	0.48–1.61			

n = 270 (excluding 30 patients lost to follow-up).
BMI, body mass index; CI, confidence interval; HIN, high-grade intraepithelial neoplasia; HP, *Helicobacter pylori*; LIN, low-grade intraepithelial neoplasia; OR, odds ratio; PPI, proton pump inhibitor.
[a]$P < 0.05$, difference was statistically significant.

Table 6. Logistic regression analysis of factors influencing ulcer improvement postendoscopic submucosal dissection

Factors	Univariate analysis (n = 270)					Multivariate analysis (n = 270)		
	Ulcer not improved	Ulcer improved	*P*-value	OR	95% CI	*P*-value	OR	95% CI
Age, ≥60/<60	10/13	130/117	0.401	1.44	0.61–3.42			
BMI, ≥23.25/<23.25	11/12	111/136	0.790	0.89	0.38–2.10			
HP infection, yes/no	4/11	47/104	0.721	1.24	0.38–4.11			
Lesion site, gastric antrum/others	14/9	118/129	0.229	0.59	0.25–1.41			
Pathological grade, cancer + HIN/LIN + others	16/7	143/104	0.277	0.60	0.24–1.52			
Initial maximum diameter, ≥35.5/<35.5	15/8	97/150	0.016[a]	0.35	0.14–0.84	0.015[a]	0.34	0.14–0.81
Initial perpendicular line of maximum diameter, ≥27.29/<27.29	15/8	104/143	0.033[a]	0.39	0.16–0.95			
Initial ulcer area, ≥1,084.45/<1,084.45	14/9	85/162	0.012[a]	0.34	0.14–0.81			
Underlying disease, yes/no	12/11	134/113	0.848	1.09	0.46–2.56			
Gender, male/female	19/4	168/79	0.147	2.23	0.74–6.78			
(PPI + rebamipide)/PPI	8/15	129/118	0.109	2.05	0.84–5.01			

n = 270 (excluding 30 patients lost to follow-up).
BMI, body mass index; CI, confidence interval; HP, HIN, high-grade intraepithelial neoplasia; *Helicobacter pylori*; LIN, low-grade intraepithelial neoplasia; OR, odds ratio; PPI, proton pump inhibitor.
[a]$P < 0.05$, difference was statistically significant.

At 4 weeks, the ulcer improvement rates in the experimental and control groups were 94.2% and 88.7%, respectively. However, the rates of ulcer area reduction were 0.97 ± 0.034 and 0.94 ± 0.078 in the experimental and control groups, respectively, and this difference between the 2 groups was statistically significant. Therefore, combination therapy promoted ulcer healing more successfully than monotherapy. This conclusion is consistent with the results of previous studies. The ulcer healing at week 4 was less than 21%, indicating that the course for therapy should be longer than 4 weeks. The ulcer healing rates for initial maximum diameter ≥35.5 mm and <35.5 mm at week 8 were 84.6% and 94.7% ($P < 0.007$), indicating that initial maximum diameter of ulcer is an important factor for healing of post-ESD ulcer and 8 weeks' treatment is recommended. Whether the conventional ulcer classification system proposed by Sakita (13) was suitable to be employed in this study needs discussion. This classification system is a valuable guide for the clinical treatment and prognosis of ulcers, but it is not objective or continuous. Moreover, the distinction between A- and H-stage ulcers is not clear. Therefore, a new method is required to improve the evaluation of post-ESD ulcers, particularly giant iatrogenic ulcers.

Numerous factors may influence post-ESD ulcer healing, including ulcer area, ulcer site, pathological grade, blood coagulation status, Hp infection, and other comorbidities. However, studies investigating post-ESD ulcer healing have not achieved consensus regarding the importance of these factors. Our study showed that the combination therapy and lesions located in the gastric antrum were both positively associated with the ulcer healing. Oh et al. (18) showed that the degree of ulcer healing within 4 weeks was determined by the initial size of the ulcer. Similarly, Nakamura et al. (15) also suggested that the initial size of the ulcer and the location of lesion could affect healing of post-ESD ulcer, which supports our results. Therefore, the longer course of treatment should be taken for the bigger initial size of the post-ESD ulcer.

The most significant complication that occurs during post-ESD ulcer healing is bleeding. In our study, the overall incidence of bleeding was 5.33%, which was far lower than the results reported in the foreign literature (13%–38%) (19). The most likely explanation for this is the significant reduction in the incidence of bleeding that has occurred in recent years as endoscopy instruments have improved allowing the coagulation of blood vessels using hot biopsy forceps. In this study, the overall incidences of bleeding in control and experimental groups were 7.14% and 4.17% with no significant difference.

The reasons for choosing to evaluate rebamipide and the PPI lansoprazole were as follows. First, antacids are still the most effective treatment for post-ESD ulcers (20), and several studies have shown that the clinical efficacy of PPIs is superior to that of H2RAs. Second, PPIs combined with a mucosal protective agent is better able to promote ulcer healing compared to PPI monotherapy. A meta-analysis that included 11 randomized controlled trials indicated that the clinical efficacy of combination therapy is superior to PPI monotherapy (16). Finally, rebamipide has more significant effects on the healing of post-ESD ulcers than other mucosal protective agents (16). It may act by promoting the expression of gastric mucosal protective factors (Prostaglandin E and Cyclooxygenase 2), promoting the synthesis of various growth factors (epidermal growth factor [EGF], EGF receptor, and vascular endothelial growth factor), inhibiting gastric mucosal injury factors, inhibiting Hp adherence to endothelial cells, inhibiting the production of interleukin 8/leukotriene B4, or inhibiting the expression of adhesion molecules CD11b/CD18 and intercellular cell adhesion molecule-1.

In the preliminary stages of this trial, we tested 3 methods for ulcer diameter measurement: direct measurement through the endoscope biopsy channel using an endoscopic measuring instrument (Olympus, Tokyo, Japan); measurement by comparison with a visual reference (a paper disk) using Amedicom System image analysis software for image distance measurements; direct measurement

of the post-ESD specimens. Similar studies from abroad commonly apply the first method of measurement (17). However, during the resection operation, the large size of the post-ESD ulcers made it difficult to visualize them within a single field. Moreover, the ulcers were not located in the same plane. Hence, the first 2 methods lacked the accuracy required for the measurement of such ulcers. Therefore, we chose to use the resected specimen measurement as a surrogate for the measurement of the corresponding post-ESD ulcer. However, because of the drastically reduced sizes of the ulcers 4 and 8 weeks postoperatively, we were able to employ the second method and obtain relatively accurate measurements.

In conclusion, both the PPI monotherapy and the PPI plus rebamipide treatments ended up with low post-ESD ulcer healing rates in the first 4 weeks of postoperative treatment. After 8 weeks of treatment, over 90% of ulcers were in the healing or scarring stage. Compared with lansoprazole alone, rebamipide combined with lansoprazole significantly accelerated the rate of ulcer reduction but did not improve the rate of ulcer healing at 4 weeks of therapy.

CONFLICTS OF INTEREST

Guarantor of the article: Yunsheng Yang, MD.

Specific author contributions: Bin Yan and Zhongsheng Lu contributed equally to this work. Yunsheng Yang designed research. Zhongsheng Lu, Zhizheng Ge, Side Liu, Xuegang Guo, Dean Tian, Yuxiu Yang, Xiaobo Li, Wei Gong, Zhiguo Liu, Mei Liu, Bingxi Zhou, Kabing Zhao, and Jing Yang performed research. Bin Yan and Fei Pan analyzed data. Bin Yan wrote the paper.

Financial support: Nursery Science and Technology Innovation Fund of Chinese PLA General Hospital, no: 13KMM02, 18KMM02.

Potential competing interests: The authors declare no conflict of interest.

Study Highlights

WHAT IS KNOWN

- ✓ ESD induced deep and large gastrointestinal ulcers, resulted in an increased risk of perforation, bleeding, and abdominal pain.
- ✓ The optimal treatment for ESD-induced ulcers is unknown.

WHAT IS NEW HERE

- ✓ The rebamipide and lansoprazole combination therapy accelerates the reduction rate of post-ESD ulcer compared with the lansoprazole monotherapy at 4 weeks of therapy.

TRANSLATIONAL IMPACT

- ✓ Our data provide the evidence that rebamipide can significantly promote the reduction rate of post-ESD ulcer at 4 weeks of therapy.

REFERENCES

1. Gotoda T, Kondo H, Ono H, et al. A new endoscopic mucosal resection procedure using an insulation-tipped electrosurgical knife for rectal flat lesions: Report of two cases. Gastrointest Endosc 1999;50:560–3.
2. Ono H, Kondo H, Gotoda T, et al. Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001;48:225–9.
3. Isomoto H, Shikuwa S, Yamaguchi N, et al. Endoscopic submucosal dissection for early gastric cancer: A large-scale feasibility study. Gut 2009;58:331–6.
4. Kakushima N, Fujishiro M, Kodashima S, et al. Histopathologic characteristics of gastric ulcers created by endoscopic submucosal dissection. Endoscopy 2006;38:412–5.
5. 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;21:1586–9.
6. Kakushima N, Tanaka M, Sawai H, et al. Gastric obstruction after endoscopic submucosal dissection. United Eur Gastroenterol J 2013;1:184–90.
7. Nonaka K, Miyazawa M, Ban S, et al. Different healing process of esophageal large mucosal defects by endoscopic mucosal dissection between with and without steroid injection in an animal model. BMC Gastroenterol 2013;13:72.
8. Arakawa T, Higuchi K, Fujiwara Y, et al. 15th anniversary of rebamipide: Looking ahead to the new mechanisms and new applications. Dig Dis Sci 2005;50(Suppl 1):S3–11.
9. Takayama M, Matsui S, Kawasaki M, et al. Efficacy of treatment with rebamipide for endoscopic submucosal dissection-induced ulcers. World J Gastroenterol 2013;19:5706–12.
10. 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.
11. 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;45:285–90.
12. Kobayashi M, Takeuchi M, Hashimoto S, et al. Contributing factors to gastric ulcer healing after endoscopic submucosal dissection including the promoting effect of rebamipide. Dig Dis Sci 2012;57:119–26.
13. Sakita T. Endoscopic diagnosis of gastric cancer. Gan No Rinsho 1972: Suppl:108–14. [Japanese]
14. Asakuma Y, Kudo M, Matsui S, et al. Comparison of an ecabet sodium and proton pump inhibitor (PPI) combination therapy with PPI alone in the treatment of endoscopic submucosal dissection (ESD)—Induced ulcers in early gastric cancer: Prospective randomized study. Hepatogastroenterology 2009;56:1270–3.
15. Nakamura K, Ihara E, Akiho H, et al. Limited effect of rebamipide in addition to proton pump inhibitor (PPI) in the treatment of post-endoscopic submucosal dissection gastric ulcers: A randomized controlled trial comparing PPI plus rebamipide combination therapy with PPI monotherapy. Gut Liver 2016;10:917–24.
16. Nishizawa T, Suzuki H, Kanai T, et al. Proton pump inhibitor alone vs proton pump inhibitor plus mucosal protective agents for endoscopic submucosal dissection-induced ulcer: A systematic review and meta-analysis. J Clin Biochem Nutr 2015;56:85–90.
17. Shin WG, Kim SJ, Choi MH, et al. Can rebamipide and proton pump inhibitor combination therapy promote the healing of endoscopic submucosal dissection-induced ulcers? A randomized, prospective, multicenter study. Gastrointest Endosc 2012;75:739–47.
18. 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;54:1494–9.
19. Yamamoto H, Sekine Y, Higashizawa T, et al. Successful en bloc resection of a large superficial gastric cancer by using sodium hyaluronate and electrocautery incision forceps. Gastrointest Endosc 2001;54:629–32.
20. Fujishiro M, Chiu PW, Wang HP. Role of antisecretory agents for gastric endoscopic submucosal dissection. Dig Endosc 2013;25(Suppl 1):86–93.
21. 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;102:1610–6.
22. Yang Z, Wu Q, Liu Z, et al. Proton pump inhibitors versus histamine-2-receptor antagonists for the management of iatrogenic gastric ulcer after endoscopic mucosal resection or endoscopic submucosal dissection: A meta-analysis of randomized trials. Digestion 2011;84:315–20.
23. Arakawa T, Kobayashi K, Yoshikawa T, et al. Rebamipide: Overview of its mechanisms of action and efficacy in mucosal protection and ulcer healing. Dig Dis Sci 1998;43:5S–13S.
24. Tarnawski AS, Chai J, Pai R, et al. Rebamipide activates genes encoding angiogenic growth factors and Cox2 and stimulates angiogenesis: A key to its ulcer healing action? Dig Dis Sci 2004;49:202–9.