Original Article

Vonoprazan vs lansoprazole for the treatment of artificial gastric ulcer after endoscopic submucosal dissection: a prospective randomized comparative study

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Vonoprazan is a potent inhibitor of gastric acid secretion and may have better response than proton pump inhibitors (PPIs) in the treatment of endoscopic submucosal dissection induced artificial ulcers. However, reported outcomes remain controversial. In this study, we conducted a prospective, randomized comparative trial to evaluate healing effects of vonoprazan and lansoprazole on endoscopic submucosal dissection (ESD)-induced ulcers. We enrolled 216 patients who underwent endoscopic submucosal dissection for early gastric neoplasms. They were randomly divided into vonoprazan (20 mg/day) and lansoprazole (30 mg/day) groups. The primary endpoint was the reduction rate of ulcer and complete healing (scar) ratio of ESD-induced ulcers at 4 and 8 weeks. Finally, 101 patients of the vonoprazan group and 95 patients of the lansoprazole group were included in the analysis. There were no significant differences in the reduction rate between the vonoprazan and lansoprazole groups at either timepoint (4 weeks, 94.0 vs 93.4%; 8 weeks, 99.8 vs 99.9%, respectively). The complete healing ratio at 4 and 8 weeks did not differ significantly between the vonoprazan and lansoprazole groups (4 weeks, 11.9 vs 12.6%; 8 weeks, 87.1 vs 86.3%, respectively). In the anti-*H. pylori*-antibody negative or positive patients, there were no significant differences in the reduction rate and complete healing ratio between the vonoprazan and lansoprazole groups. Regardless of treatment choice, the overall complete healing ratio at 8 weeks was significantly higher in the anti-*H. pylori*-antibody negative patients than the positive patients ($p = 0.006$). The healing effects of vonoprazan on ESD-induced ulcers were comparative to those of lansoprazole.

***Key Words*: vonoprazan, lansoprazole, ESD**

Endoscopic submucosal dissection (ESD) has been widely accepted and applied for the treatment of early gastric cancer.[1,2] However, ESD-induced artificial ulcer is one of major factors affecting patient recovery. For example, patients sometimes experience delayed bleeding from ESD-induced ulcer.[1] It has been reported that healing of ESD-induced ulcer is associated with various factors, such as tumor location, tumor size, submucosal fibrosis, electrocoagulation time during ESD, and mucosal atrophy with *Helicobacter pylori* (*H. pylori*) infection.[3–5]

The use of gastric acid inhibitors is recommended after ESD,[1,6] because gastric acid inhibition prevents bleeding and improve the healing of ESD-induced ulcers.[6] Proton pump inhibitors (PPIs) are widely used to treat acid-related disorders such as gastric and duodenal ulcers and gastroesophageal reflux disease and are also useful for treatment of ESD-induced ulcers.[6–9] To achieve more potent and sustained gastric acid suppression, potassium-competitive acid blockers (P-CABs) have been developed.[10,11] Similar to PPIs P-CABs inhibit gastric H^+, K^+-ATPase, but unlike PPIs P-CABs inhibit the enzyme in a K^+-competitive manner.[12] Vonoprazan is an orally active P-CAB, which exerts faster, more potent, sustained suppression of gastric acid secretion than PPIs.[10,11,13] As compared to PPIs, the acid-inhibitory effects of vonoprazan are less influenced by CYP2C19 genotypes compared to PPIs.[11]

It was suggested that vonoprazan may have comparable or better response than PPIs in the treatment of ESD-induced ulcers. Some previous studies reported that vonoprazan induced faster healing of ESD-induced ulcers than PPI.[14,15] We have also reported a preferable effect of vonoprazan in a small size preliminary study.[16] There is a growing number of reports comparing the effectiveness of vonoprazan with that of PPIs in treating ESD-induced ulcers,[6,17,18] but reported outcomes are still controversial. In this study, we demonstrate the results of a prospective, randomized comparative trial of large sample size to evaluate healing effects of vonoprazan and lansoprazole (PPI) on ESD-induced artificial ulcers.

Patients and Methods

Patients. We enrolled 216 patients who were scheduled to undergo ESD for gastric neoplasm at the Shiga University of Medical Science Hospital from September 2015 to August 2018. Inclusion criteria were age >20 years and the diagnosis of gastric adenoma or early-stage gastric cancer. Early-stage gastric cancers were clinically diagnosed using endoscopy, endoscopic ultrasonography, histopathology, and computed tomography. The criteria of early-stage gastric cancer was used according to a previous report.[19] Patients with advanced-stage gastric cancer were excluded. Written informed consent was obtained from all patients, and approval for the study protocol was given in advance by the Institutional Review Board of the Shiga University of Medical Science (Number: 27-36). This trial was registered in the University Hospital Medical Information Network, UMIN 000018188.

Study design. This study was a prospective, randomized trial to clarify clinical and pharmacological parameters influencing the

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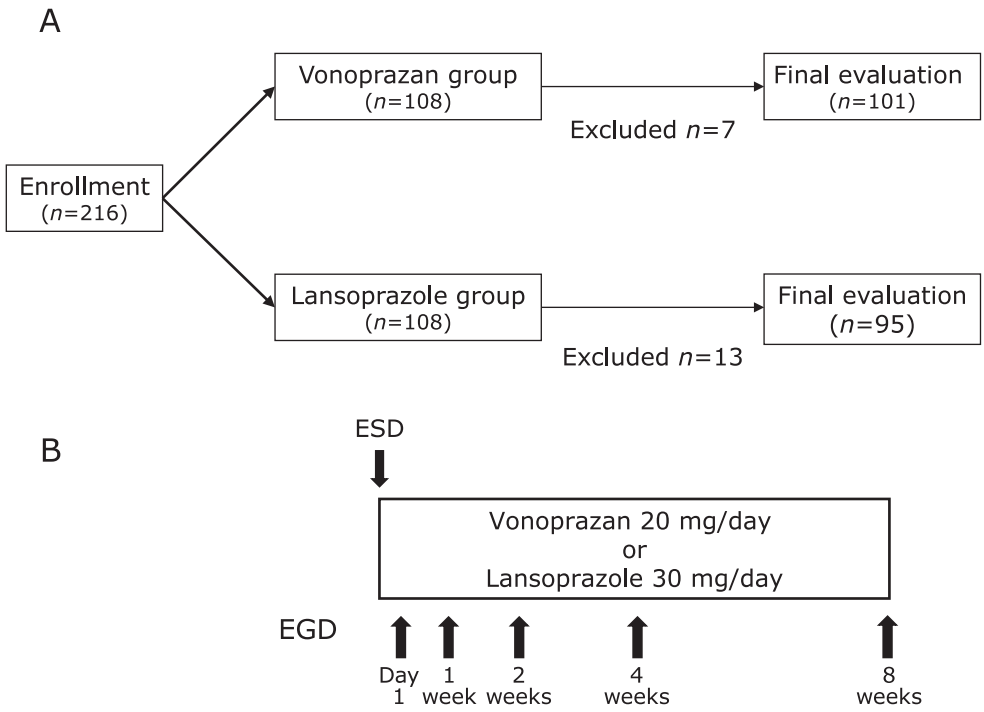

Fig. 1. Study design. (A) Flow diagram of randomization to the vonoprazan and lansoprazole groups. A total of 216 patients were enrolled. We excluded 7 patients from the vonoprazan group and 13 patients from the lansoprazole group. Reasons for exclusion are described in the text. Finally, we analyzed 101 patients in the vonoprazan group and 95 patients in the lansoprazole group. (B) After surgery, oral administration of vonoprazan (20 mg/day) or lansoprazole (30 mg/day) was started and continued for 8 weeks. Endoscopic examination was performed on the day post-ESD and at 2, 4, 6, and 8 weeks later. ESD, endoscopic submucosal dissection; EGD, esophagogastroduodenoscopy.

healing of ESD-induced artificial ulcers. Using the minimization method based on location of the tumor (upper, middle or lower third of the stomach) and tumor size (≤20 mm or >20 mm), we randomized patients to receive vonoprazan 20 mg/day for 8 weeks (n = 108) or lansoprazole 30 mg/day for 8 weeks (n = 108) (Fig. 1).

ESD. ESD was performed with a single channel endoscope (GIF-H290Z; Olympus, Tokyo, Japan). We used a dual knife (KD-650; Olympus) as the cutting device, and an electrical current was applied using an electrosurgical generator (VIO300D; ERBE Elektromedizin GmbH, Tubingen, Germany). Visible vessels were heat-coagulated using hemostatic forceps (Coagrasper G; FD-412LR; Olympus).

Major and minor axes of ESD-induced artificial ulcers were endoscopically measured with measurement forceps (M2-4K; Olympus) at 1 day and 1, 2, 4, and 8 weeks after ESD. The area of artificial ulcers was calculated as the area of a prolate ellipse.

***H. pylori* infection.** *H. pylori* infection status was determined with an anti-*H. pylori* IgG serological test (E plate Eiken *H. pylori* antibody®; Eiken Chemical Co. Ltd., Tochigi, Japan). We used a cut-off value 10 U/ml for anti-*H. pylori* antibody positiveness.[20]

Outcomes. The primary endpoints were the ulcer reduction rate and complete healing ratio of ESD-induced ulcers at 4 and 8 weeks post-ESD. The ulcer reduction rates were calculated as (the area of resected specimen – the artificial ulcer area)/the area of resected specimen × 100 (%). Complete healing was defined by achievement of scar staging (complete closure and 100% reduction rate). The secondary endpoint was delayed bleeding, which was defined as bleeding episodes that required endoscopic hemostasis within 4 weeks post-ESD.

Statistical analysis. Age, body weight, body mass index, HbA1c, ESD procedure time, and area of resected specimen are expressed as mean ± SD. Statistically significant differences in these parameters were determined using one-way ANOVA with Scheffé multiple comparison and Fisher's exact tests. All p values are two-sided, and $p<0.05$ was considered statistically significant. Calculations were performed using commercial software (SPSS ver. 20; IBM Inc., Armonk, NY).

Results

Of 216 patients, 108 patients were randomized to the vonoprazan group and 108 were randomized to the lansoprazole group. Finally, 101 patients of the vonoprazan group and 95 patients of the lansoprazole group were included in the analysis (Fig. 1). There were no significant differences in demographic or clinical characteristics of gastric neoplasms between the vonoprazan and lansoprazole groups (Table 1). The reasons for analysis exclusion in the vonoprazan group were surgical treatment (n = 1), perforation (n = 1), bleeding (n = 1), pneumonia (n = 2) and follow-up failure (n = 2), and those in the lansoprazole group were surgical treatment (n = 3), bleeding (n = 2) and follow-up failure (n = 8). Tumor characteristics determined post-ESD are detailed in Table 2, and they were not significantly different between the two groups.

Table 3 shows sequential changes of the ulcer reduction rate of ESD-induced ulcer. There were no significant differences in the reduction rate between the vonoprazan and lansoprazole groups at either timepoint (4 weeks, 94.0 vs 93.4%; 8 weeks, 99.8 vs 99.9%, respectively) (Table 3A). A previous study has reported that *H. pylori* infection affects the healing of the ESD-induced ulcer[4] so the reduction rate was analyzed in the anti-*H. pylori*-antibody negative or positive patients. However, there were no significant differences in the reduction rate between the vonoprazan and lansoprazole groups in the anti-*H. pylori*-antibody negative or positive patients at any every point (Table 3B and C).

Table 4 shows the achievement of complete healing (scar). The

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Table 1. Demographic and basic characteristics of patients

	Vonoprazan group	Lansoprazole group	*p* value
Number, *n*	101	95	
Age (years)	71.5 ± 8.8	71.2 ± 8.6	0.77
Sex (male:female)	76:25	69:26	0.68
Body weight (kg)	60.1 ± 10.9	59.3 ± 10.5	0.73
BMI (kg/m^2)	22.9 ± 2.9	22.8 ± 2.6	0.3
Drugs, *n* (%)			
Anticoagulants	28 (28)	31 (33)	0.45
Antihypertensive drugs	63 (62)	53 (56)	0.35
Hypoglycemic drugs	16 (16)	15 (16)	0.99
Cholesterol-lowering agents	23 (23)	29 (31)	0.22
HbA1c (%)	6.02 ± 0.61	5.99 ± 0.57	0.47
H. pylori-positive *n* (%)	34 (34)	28 (29)	0.53

Table 2. Characteristics of resected tumors

	Vonoprazan group (*n* = 101)	Lansoprazole group (*n* = 95)	*p* value
Histopathology, *n* (%)			0.84
Adenoma	18 (17.8)	14 (14.7)	
Differentiated carcinoma	82 (81.2)	80 (84.2)	
Undifferentiated carcinoma	1 (1.0)	1 (1.1)	
Tumor depth, *n* (%)			0.56
m	90 (89.1)	85 (89.5)	
sm1	8 (7.9)	5 (5.3)	
sm2	3 (3.0)	5 (5.3%)	
Tumor location, *n* (%)			0.24
upper	8 (7.9)	10 (10.5)	
middle	32 (31.7)	39 (41.1)	
lower	61 (60.4)	46 (48.4)	
Area of resected specimen (mm^2)	762.7 ± 524.2	817.6 ± 659.7	0.52
Complication, *n* (%)			
Delayed bleeding	2 (2.0)	3 (3.2)	0.6
Perforation	3 (3.0)	2 (2.1)	0.7

Table 3. Reduction rates of artificial ulcer

(A) Total

	1 week	2 weeks	4 weeks	8 weeks
VPZ (*n* = 101) %	37.8 ± 32.8	73.9 ± 19.4	94.0 ± 6.2	99.8 ± 1.0
LPZ (*n* = 95) %	30.2 ± 34.0	69.4 ± 24.7	93.4 ± 8.1	99.9 ± 0.5
p value	0.11	0.6	0.37	0.88

(B) Anti-*H. pylori* antibody negative

	1 week	2 weeks	4 weeks	8 weeks
VPZ (*n* = 67) %	41.3 ± 33.1	73.2 ± 21.0	94.0 ± 6.8	99.8 ± 1.0
LPZ (*n* = 67) %	31.1 ± 36.6	70.2 ± 27.7	93.4 ± 8.5	99.8 ± 0.6
p value	0.09	0.49	0.79	0.68

(C) Anti-*H. pylori* antibody positive

	1 week	2 weeks	4 weeks	8 weeks
VPZ (*n* = 34) %	31.1 ± 31.8	75.3 ± 16.2	93.8 ± 5.1	99.7 ± 0.9
LPZ (*n* = 28) %	28.3 ± 27.4	67.5 ± 15.8	93.4 ± 7.0	99.9 ± 0.3
p value	0.71	0.06	0.79	0.3

VPZ, vonoprazan; LPZ, lansoprazole.

complete healing ratio at 4 and 8 weeks did not differ significantly between the vonoprazan and lansoprazole groups (4 weeks, 11.9 vs 12.6%; 8 weeks, 87.1 vs 86.3%, respectively) (Table 4A). These results were also observed in the anti-*H. pylori*-antibody negative or positive patients (Table 4B and C). Regardless of treatment choice however, the overall complete healing ratio was significantly higher in the *H. pylori*-negative patients than in the positive patients at 8 weeks (positive 74.2% vs negative 89.6%, $p = 0.006$) (Table 4D).

Two patients of the vonoprazan group and 3 patients in the

Table 4. Achievement of complete healing (scar)

(A) Total

	VPZ (*n* = 101)	LPZ (*n* = 95)	*p* value
4 weeks	11.90%	12.60%	0.87
8 weeks	87.10%	86.30%	0.87

(B) Anti-*H. pylori* antibody-negative

	VPZ (*n* = 67)	LPZ (*n* = 67)	*p* value
4 weeks	13.40%	14.90%	0.8
8 weeks	89.50%	89.50%	1

(C) Anti-*H. pylori* antibody-positive

	VPZ (*n* = 34)	LPZ (*n* = 28)	*p* value
4 weeks	8.80%	7.10%	0.81
8 weeks	82.60%	78.60%	0.71

(D) Anti-*H. pylori* antibody (Ab) status

	HP-Ab positive (*n* = 62)	HP-Ab negative (*n* = 134)	*p* value
4 weeks	8.10%	14.20%	0.22
8 weeks	74.20%	89.60%	0.006

HP, *Helicobacter pylori*.

lansoprazole group experienced delayed bleeding, and there was no significant difference between the two groups.

Discussion

This prospective randomized study was conducted to compare the effects of vonoprazan and lansoprazole on ulcer healing and preventing delayed bleeding after ESD for early gastric neoplasm. Many reports have compared vonoprazan with PPIs in terms of healing of ESD-induced ulcers[6] and some have reported that vonoprazan is superior to PPIs in this respect.[14,15] However, we could not find any significant differences between vonoprazan and lansoprazole in the healing effects on ESD-induced ulcers and preventing delayed bleeding.

Vonoprazan or PPIs are used for inducing the rapid healing of ESD-induced gastric ulcers.[6] Because vonoprazan exerts more rapid and potent effects on elevating the intragastric pH than PPIs,[10] it can be assumed that vonoprazan induces ulcer healing more rapidly and prevents bleeding episodes more efficiently than PPIs after ESD. Maruoka *et al.*[14] reported that vonoprazan was superior to esomeprazole in the healing of ESD-induced ulcers at 4 weeks. Similarly, Tsuchiya *et al.*[15] reported from a prospective randomized controlled trial that vonoprazan was more effective in healing of ESD-induced ulcer at 8 weeks than esomeprazole. In the preliminary data from a small sample size study, we also observed a preferable effects of vonoprazan on the healing of ESD-induced ulcer at 2 weeks.[16] On the other hand, Takahashi *et al.*[21] prospectively compared the healing effects of vonoprazan and lansoprazole on ESD-induced ulcers at 4 weeks, but could not detect any significant differences. Hirai *et al.*[17] compared the healing effects of vonoprazan and lansoprazole through a prospective large-scale study, but ulcer healing at 4 and 8 weeks and delayed bleeding did not differ significantly. In this study, we were also unable to detect any significant differences between vonoprazan and lansoprazole at 4 and 8 weeks. Despite some differences in study design and patients' characteristics, our study design was quite similar to the study conducted by Hirai *et al*.[17] Both studies are relatively large-scale, prospective, randomized comparative studies and evaluated the healing effects of monotherapy of vonoprazan and lansoprazole at 4 and 8 weeks. Similar results to these studies strongly suggest that vonoprazan and lansoprazole are comparable in the healing of ESD-induced artificial ulcers and preventing delayed bleeding.

Recently, Kang *et al.*[6] performed a meta-analysis of the healing effects of vonoprazan and PPIs on ESD-induced ulcer. They analyzed a total of 1,265 patients from 12 studies and reported that the healing rate at 4 weeks was significantly higher in the vonoprazan group than in the PPI group but that at 8 weeks it was significantly higher in the PPI group. There was no evidence of significant difference in delayed bleeding. Based on these results, they concluded that there is no substantial difference in ulcer healing and post-ESD bleeding between vonoprazan and PPIs. These data are almost compatible with our results. A higher healing rate at 4 weeks suggests that vonoprazan may have more rapidly and effectively treated artificial ulcers after ESD than did PPIs, since vonoprazan induces acid-suppressing effects more rapidly than PPIs. We also observed such a response in a previous study with a small sample size,[16] but the same response was not evident here with a larger sample size.

H. pylori infection is a major factor contributing to the pathogenesis of peptic ulcers,[22] and eradication therapy accelerates ulcer healing and reduces ulcer recurrence.[23] In contrast, some studies have shown that *H. pylori* does not influence the healing of ESD-induced artificial ulcer.[24,25] In this study, we observed that the complete healing rate at 4 weeks tended to be higher in the anti-*H. pylori* antibody-negative patients than the antibody-positive patients, and that complete healing at 8 weeks was significantly higher in the anti-*H. pylori* antibody-negative patients. In contrast, the ulcer reduction rate was not affected by anti-*H. pylori* antibody status (statistical data not shown), and the healing effects of vonoprazan and lansoprazole were comparable in the presence or absence of the *H. pylori* antibody. Our results suggest that *H. pylori* status may affect the final stage of mucosal repair which is an important step to achieving complete healing of ESD-induced ulcers. The precise role of *H. pylori* infection in the molecular mechanism of healing of artificial ulcer should be investigated in the future.

The current study has some limitations. First, this study was performed at a single center and a larger sample size would have been desirable. A multicenter study with a large sample size will be required in the future. Second, we used anti-*H. pylori* antibody for the detection of *H. pylori* infection. However, testing anti-*H. pylori* IgG cannot differentiate active or cured infection of *H. pylori* because antibody levels persist for a long period even after cure.[26] To define the association between *H. pylori* infection and the healing of ESD-induced ulcers, use of diagnostic tests such as urease test and/or biopsy culture should be considered in future studies. Third, we did not perform genomic analysis of

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the CYP2C19 gene which affects PPI metabolism.[24] Because keeping high gastric pH is difficult in patients carrying the CYP2C19 rapid metabolizing genotype, healing of the ulcer may be delayed. Future studies should therefore consider and include CYP2C19 genotyping.

In conclusion, there was no significant difference between vonoprazan and lansoprazole in the healing of ESD-induced artificial ulcers. Because vonoprazan has a stronger acid-suppressive activity than PPIs and its metabolism is not affected by CYP2C19 polymorphism, vonoprazan may be preferable in patients carrying the CYP2C19 rapid metabolizing genotype. A further large-scale prospective study with these patients is needed to make a definitive conclusion.

Author Contributions

HR, OI, and AA conceived the project, and HR, OI, MM, TO, MO, HM, SB, AA designed and supervised the experiments, interpreted results, and wrote the paper with input from all other authors. HB and TO performed endoscopy and data analysis.

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Conflict of Interest

No potential conflicts of interest were disclosed.

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