Efficacy of Vonoprazan for Refractory Reflux Esophagitis after Esophagectomy

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Keywords

Vonoprazan · Proton-pump inhibitor · Reflux esophagitis · Esophagectomy · Acid reflux

Abstract

Background: Refractory reflux esophagitis (RRE), unresponsive to conventional proton-pump inhibitors (PPIs), is a complication in esophagectomy with gastric pull-up. Vonoprazan (VPZ), a novel potassium-competitive acid blocker, has been available in Japan since 2015. Here, we investigated the efficacy of VPZ on PPI-resistant RRE after esophagectomy with gastric pull-up. **Methods:** This was a single-center retrospective study. We used the revised Los Angeles (r-LA) classification based on the Los Angeles classification and the modified Los Angeles classification to evaluate abnormal forms of mucosal breaks such as lateral spreading consistently. Patients who underwent esophagectomy with gastric pull-up and had RRE grade B–D as per the r-LA classification, despite using standard-dose PPIs or double dose of rabeprazole, were included. Sixteen patients who switched to VPZ (20 mg/day) and 14 patients who continued PPIs were as-

signed to the VPZ and PPI groups, respectively. Endoscopic observations were reviewed by 3 endoscopists using the r-LA classification to ensure consistent diagnosis, while the treatment arm and patient information were blinded to evaluators. We defined mucosal breaks that improved by at least one grade after treatment as improved mucosa and recovery to grade M or N as mucosal healing. **Results:** The percentage of patients with improved mucosa in the VPZ and PPI groups was 81.3 and 14.3%, respectively ($p < 0.001$). The rate of mucosal healing was 68.8 and 7.1%, respectively ($p = 0.001$). **Conclusion:** VPZ significantly improved PPI-resistant RRE after esophagectomy with gastric pull-up.

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Introduction

Esophagectomy with gastric pull-up is the standard treatment for patients with esophageal carcinoma. However, reflux esophagitis (RE), a common complication after esophagectomy with gastric pull-up [1, 2], can deteriorate patients' quality of life and can lead to aspiration

Fig. 1. Representative image of r-LA classification grade B (a) and grade C (b). Grade B was defined as a mucosal break with a major length of more than 5 mm, in which the maximum circumference did not exceed one-sixth of the total circumference, while grade C was defined as a mucosal break that exceeded one-sixth of the total circumference, but less than three-fourth of it. r-LA, revised Los Angeles.

pneumonia. Generally, the first-line treatment for RE is the administration of standard-dose proton-pump inhibitors (PPIs). Approximately 90% of patients with mild RE, and 80–85% with severe RE, are successfully treated by them [3, 4]. However, a recent study from Japan reported that the incidence of standard-dose PPI-resistant RE has increased [5]. Severe RE has also been observed in patients after esophagectomy with gastric pull-up. RE after esophagectomy is usually treated with PPIs [6] like the patients without history of esophagectomy; however, refractory reflux esophagitis (RRE), which is intractable to standard-dose PPIs, is sometimes observed. Many acid reflux events and strong acid exposure due to direct anastomosis to the stomach may be the major reasons for the observation. More than 80% of the holding time to maintain stomach pH at 4 or higher is required to secure the healing in RE endoscopically [7].

Vonoprazan (VPZ), a novel potassium-competitive acid blocker that blocks H^+ , K^+ ATPase in a competitive and reversible manner [8], has been available in Japan since 2015. The effect of VPZ can last longer than that of the original PPIs, and it remains stable without acidic conditions [9]. It has been reported that 87.5% of patients with PPI-resistant RE have been successfully treated by a dosage of 20 mg/day of VPZ [4]. Therefore, it can be hypothesized that VPZ might be effective in the treatment of RRE after esophagectomy. Hence, the main purpose of this study was to elucidate the efficacy of VPZ on RRE in patients after esophagectomy with gastric pull-up.

Materials and Methods

Study Design

This study was a single-center retrospective study.

Definition of the Revised Los Angeles Classification

To review the endoscopic findings retrospectively, we used revised criteria to diagnose the severity of RE based on the Los Angeles (LA) classification [10] and the modified Los Angeles (m-LA) classification [11], because mucosal breaks in patients after esophagectomy with gastric pull-up sometimes presented abnormal forms such as lateral spreading, which made diagnoses of severity difficult. The revised criteria were based on the revised Los Angeles (r-LA) classification, and the grades were as follows. Grade B was defined as a mucosal break with a major length of more than 5 mm, in which the maximum circumference did not exceed one-sixth of the total circumference (Fig. 1a), and grade C was defined as a mucosal break that exceeded one-sixth of the total circumference, but less than three-fourth of it (Fig. 1b). We used the same criteria as those of the LA and m-LA classification to define grades N, M, A, and D.

Patients

Patients who underwent esophagectomy because of esophageal cancers underwent esophagogastroduodenoscopy (EGD) once or twice a year in Toranomon Hospital. A total of 682 patients underwent EGD after esophageal surgery between January 2012 and December 2016. Among the patients who underwent esophagectomy with gastric pull-up, those who met the following 3 criteria were included: EGD was conducted between January 2012 and December 2016, VPZ was administered for RRE, and follow-up EGD was performed after administration of VPZ. We excluded patients who underwent esophagectomy with ileocolic reconstruction, jejunal graft reconstruction, and other operations, such as the Heller-Nissen operation, as well as patients who had RE of grade N–A as per the r-LA classification. In general, severe RE is classified as grade C and D as per the LA classification [5]; however, it is sometimes difficult to distinguish LA grade B from C accurately in patients after esophagectomy. Therefore, we considered severe RE as grade B or higher per the r-LA classification in patients with RRE after esophagectomy. As a result, 41 patients were diagnosed with RRE after esophagectomy. Among them, 21 patients shifted from PPIs to VPZ. Five patients were excluded because they did not undergo follow-up endoscopy. Finally, 16 patients who underwent EGD after the administration of VPZ were included in the VPZ group. In contrast, 20 patients continued to use PPIs. After excluding patients who did not undergo follow-up endoscopy and who discontinued PPIs on their own, 14 patients were included in the PPI group (Fig. 2). Administration of VPZ or PPIs was at the surgeon's discretion.

Fig. 2. Flow diagram of this study. r-LA, revised Los Angeles classification; PPI, proton-pump inhibitor; RRE, refractory reflux esophagitis; VPZ, vonoprazan.

PPI and VPZ Dosage

Standard-dose PPIs including lansoprazole (30 mg/day), rabeprazole (10 mg/day), and esomeprazole (20 mg/day) were used. A double dose of rabeprazole was 20 mg/day. The standard dose of VPZ for RE was 20 mg/day.

Definition of RRE after Esophagectomy and Parameters Indicating Improvement

RRE after esophagectomy was defined as failure to achieve endoscopic improvement up to the r-LA grade A after at least 8 weeks of standard-dose PPI or double dose of rabeprazole administration. Both m-LA and r-LA classification enabled categorization of

Table 1. Patient characteristics

	VPZ group (<i>n</i> = 16)	PPI group (<i>n</i> = 14)	<i>p</i> value
Gender, male (%)	13 (81.3)	11 (78.6)	1.000
Age, median [IQR], years	65 [59, 71]	66 [63, 72]	0.498
T factor, <i>n</i>	T1: 7 T2: 2 T3: 4 T4: 2 Atypical cells: 1	T1: 7 T2: 4 T3: 3 T4: 0	0.449
Neo or adjuvant therapy, <i>n</i> *	10	8	0.765
Neo adjuvant therapy, <i>n</i>	8	3	0.105
Adjuvant therapy, <i>n</i>	5	7	0.296
Radiation therapy, <i>n</i>	4	0	0.103
Reconstruction route, <i>n</i> (retrosternum:posterior mediastinum)	9:7	4 : 10	0.127
Anastomosis site, <i>n</i> (neck:intrathoracic)	16:0	14 : 0	–
Recurrence after operation, <i>n</i>	0	0	–
r-LA classification grade at the diagnosis of RRE after esophagectomy	Grade B: 7 Grade C: 8 Grade D: 1	Grade B: 7 Grade C: 7 Grade D: 0	0.626
History of balloon dilatation after operation	1	0	1.000
Atrophic gastritis before operation, <i>n</i> (%)**	2 (16.7)	6 (46.2)	0.202
Atrophy of gastric pull-up, <i>n</i> (%)	5 (31.3)	8 (57.1)	0.153
Superficial gastritis of gastric pull-up, <i>n</i> (%)	10 (62.5)	4 (28.6)	0.063
Fundic gland polyp in gastric pull-up, <i>n</i> (%)	4 (25)	2 (14.3)	0.657
Food residue in gastric pull-up, <i>n</i> (%)	7 (43.8)	6 (42.9)	0.961
Period from operation to diagnosis of RRE after esophagectomy***	52 [12, 121.8]	89.1 [49.6, 111.2]	0.257
Period from administration of PPI to diagnosis of RRE after esophagectomy***	18.2 [8.1, 111]	57.3 [36.3, 87.3]	0.294
Period from diagnosis of RRE after esophagectomy to follow-up EGD***	5.8 [5.3, 6.2]	7.9 [5.9, 12.1]	0.015
Period from administration of VPZ to follow-up EGD***	5.2 [4.7, 5.6]	–	–

VPZ, vonoprazan; PPI, proton-pump inhibitor; IQR, interquartile range; r-LA, revised Los Angeles; RRE, refractory reflux esophagitis; EGD, esophagogastroduodenoscopy. * Including duplication. ** Five patients' data were unavailable. *** Median [IQR] (months).

RRE after esophagectomy in the same way because grades N, M, and A were similarly defined under both criteria.

The parameters considered to evaluate improvement were improved mucosa and mucosal healing. Improved mucosa was defined as an improvement in mucosal breaks by more than one grade based on the r-LA classification after the administration of VPZ or under PPI treatment. Mucosal healing was defined as mucosal breaks that improved to r-LA grade M or N.

Study End Points

The primary end points were rates of improved mucosa and mucosal healing.

Methods to Evaluate Endoscopic Findings

EGD was performed via endoscopy using GIF-Q260 or GIF-H260 (Olympus Co., Tokyo, Japan) under consciousness or after administration of pethidine hydrochloride. Three endoscopists (2 board-certified experts of the Japan Gastroenterological Endoscopy Society and one trainee) reviewed the white light endoscopic images and images obtained by narrow band imaging endoscopy of 30 patients (the VPZ group; *n* = 16 and PPI group; *n* = 14) retrospectively. All images were arranged randomly; the evaluators

were blinded to the treatment arm and patient information. In the VPZ group, endoscopic findings before and after the administration of VPZ were evaluated. In contrast, endoscopic findings at RRE diagnosis and those at the next assessment were scrutinized in the PPI group. If the diagnosis by the 3 endoscopists varied, a final decision was made based on their discussion.

Statistical Analyses

χ^2 and Fisher's exact tests were used for between-group comparisons of qualitative variables, and the Mann-Whitney U test was used for the comparison of quantitative variables. All statistical analyses were performed using SPSS software for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). A *p* value <0.05 indicated statistical significance.

Additionally, we evaluated the interobserver agreement rates when the diagnoses made by 3 endoscopists matched. The Fleiss' kappa value was used to assess the degree of interobserver agreement regarding the r-LA classification.

Ethics Approval

This study was retrospective in nature and was performed according to the ethical principles of the Declaration of Helsinki for

Fig. 3. Representative image of improvement in RRE after esophagectomy upon administration of VPZ. **a** RRE with a PPI. **b** Mucosal healing at 9 months after administration of VPZ. VPZ, vonoprazan; RRE, refractory reflux esophagitis; PPI, proton-pump inhibitor.

medical research involving human subjects. The protocol was approved by the Ethics Committee of Toranomon Hospital, Japan (Protocol number 1422).

Results

Patient Characteristics

Patient characteristics are shown in Table 1. In the VPZ group, 13 patients were male and 3 were female, whereas in the PPI group, 11 were male and 3 were female. The median age at the time of diagnosis of RRE was 65 and 66 years and the median period from operation to diagnosis of RRE was 52 and 89.1 months in the VPZ and PPI group, respectively. A double dose of rabeprazole was administered to 2 and 4 patients of the VPZ and PPI group, respectively. The median interval from PPI administration until diagnosis of RRE and diagnosis of RRE until follow-up EDG were 18.2 and 5.8 months in the VPZ group and 57.3 and 7.9 months in the PPI group, respectively. The median interval from administration of VPZ until follow-up EGD was 5.2 months. No adverse events were observed after the administration of VPZ. There were no significant differences between the PPI and VPZ groups in terms of patient background, except for the period from diagnosis of RRE after esophagectomy to follow-up EGD.

r-LA Classification in Both Groups and Interobserver Agreement Rates

The severity/grades of RE at diagnosis of RRE after esophagectomy and the follow-up EGD are shown in Table 2. The interobserver agreement rate was 62.5% in the VPZ group and 53.6% in the PPI group. The overall Fleiss' kappa value was 0.56.

Table 2. r-LA classification in both groups

r-LA	VPZ group (n = 16)		PPI group (n = 14)	
	before VPZ	after VPZ	diagnosis of RRE	next EGD
Grade N	0	2	0	0
Grade M	0	9	0	1
Grade A	0	1	0	0
Grade B	7	3	7	5
Grade C	8	0	7	8
Grade D	1	1	0	0

VPZ, vonoprazan; PPI, proton-pump inhibitor; r-LA, revised Los Angeles; RRE, refractory reflux esophagitis; EGD, esophago-gastroduodenoscopy.

Table 3. Main outcomes

	VPZ group (n = 16)	PPI group (n = 14)	p value
Improved mucosa, n (%)	13 (81.3)	2 (14.3)	<0.001
Mucosal healing, n (%)	11 (68.8)	1 (7.1)	0.001

VPZ, vonoprazan; PPI, proton-pump inhibitor.

Main Outcomes

The main outcomes are shown in Table 3. The percentage of patients with improved mucosa was 81.3% (13 of 16 patients) in the VPZ group and 14.3% (2 of 14 patients) in the PPI group. The rate of mucosal healing was 68.8% (11 of 16 patients) in the VPZ group and 7.1% (1 of 14 patients) in the PPI group (Fig. 3). There were significant differences in improved mucosa ($p < 0.001$) and mucosal healing ($p = 0.001$). The proportion of improved

Table 4. Details of 16 patients in the VPZ group

r-LA grade	Age	Gender	Gastric atrophy before operation	Superficial gastritis of gastric pull-up	Atrophy of gastric pull-up	Food residue in gastric pull-up
B→N	55	M	×	×	×	×
B→M	59	M	×	○	×	×
B→M	66	M	×	○	×	○
B→M	63	M	○	○	×	×
B→M	69	F	na*	○	×	×
B→B	68	F	na*	○	×	×
B→B	78	F	×	×	○	○
C→N	58	M	○	×	○	×
C→M	48	M	na*	○	○	○
C→M	71	M	×	○	×	○
C→M	61	M	×	○	×	○
C→M	66	M	na*	×	○	○
C→M	60	M	×	×	×	○
C→A	76	M	×	○	×	×
C→B	60	M	×	○	×	×
D→D	71	M	×	×	○	×

r-LA, revised Los Angeles; M, male; F, female; VPZ, vonoprazan; na, not available. * This was because endoscopy was unable to pass through the esophageal carcinoma.

mucosa in r-LA grade B before VPZ was 71.4% (5 of 7 patients), r-LA grade C was 100% (8 of 8 patients), and r-LA grade D was 0% (0 of 1 patient) in the VPZ group (Table 4). However, 3 patients (1 male and 2 females) exhibited no changes upon endoscopic examination.

Discussion

In this retrospective study, the efficacy of VPZ on PPI-resistant RRE after esophagectomy with gastric pull-up was evaluated. A 20 mg/day dose of VPZ significantly improved mucosal breaks in 81.3% of the treated patients compared to that in patients who continued PPI use. Additionally, VPZ aided mucosal healing in 68.8% of the patients.

This is the first report to elucidate the effectiveness of VPZ on RRE after esophagectomy in the Japanese population. A previous study showed that the residual esophagus is always exposed to gastric acid and duodenal secretions, which contain bile, and this leads to erosion of the residual esophagus [12]. Therefore, patients with RRE after esophagectomy usually suffer acidic regurgitation and reflux. Our results indicate that gastric acid reflux is a major cause of RRE after esophagectomy with gastric pull-up and VPZ could be efficacious in patients who have these symptoms. In this study, 43.3% of patients had

food residues in the gastric conduit. Standard-dose PPIs usually lose their pharmaceutical effect because they are inactivated in a gastric conduit with food residues, whereas VPZ can remain active without the acidic condition. Therefore, VPZ is a good candidate to treat RRE after esophagectomy. The reason for frequently observing food residues in the gastric conduit may be due to the damage to gastropyloric motor activity as a result of the surgical procedure. It has been reported that the severity of RE decreases and antropylic motor activity usually recovers with time [13].

It has been reported that the metabolism of VPZ is not related to the CYP2C19 genotype [14]. In this study, we did not investigate the CYP2C19 genotype, but PPIs are easily eliminated during early metabolism by CYP2C19 [15]. The percentages of homo- and hetero-early metabolizers are estimated to reach approximately 35 and 46% in Japan, respectively [16]. Therefore, we speculate that VPZ had a positive effect on RRE after esophagectomy because it could fully function regardless of CYP2C19. However, we did not investigate the CYP2C19 status in the patients because CYP2C19 is not covered by national insurance, and this was a retrospective study.

In the present study, we used the r-LA classification, in which the overall Fleiss' kappa value was 0.56. Compared to the values of a previous study [17], the interobserver agreement rates in this study were moderate. Regarding

interobserver consistency in the LA classification adding healed mucosal breaks by experts [18, 19], the kappa values were 0.39 and 0.556, respectively. Therefore, we believe that our endoscopic evaluation on the severity of RE was consistent.

We noted that 3 patients showed no significant endoscopic changes after VPZ administration. These patients were older and had a shorter median interval from the operation than the other patients. Additionally, atrophy of the gastric pull-up was observed in 2 of the 3 patients. *Helicobacter pylori* infection or eradication might be related to the efficacy, but we were unable to evaluate those in this retrospective review. However, as these were the only ineffective cases, the reason why these patients showed no improvements was not determined.

The main limitation of this study is that it was a single-center, retrospective study with a small sample size. Other limitations include the use of noncontiguous patients, the lack of evaluations of subjective data including symptoms, pH monitoring, and that the administration of VPZ was decided by each attending physician. Moreover, the amount of reflux bile juice in the gastric pull-up was not determined. However, we believe the present study elucidates the promising efficacy of VPZ for RRE after esophagectomy. Further research is essential to support the results of this study. In conclusion, our study showed that VPZ could improve mucosal breaks in patients with RRE after esophagectomy with a reconstructed gastric tube.

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Statement of Ethics

This study was performed according to the ethical principles of the Declaration of Helsinki for medical research involving human subjects. The protocol was approved by the Ethics Committee of Toranomon Hospital, Japan (Protocol number 1422).

Conflict of Interest Statement

The authors declare no conflict of interests.

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Author Contributions

Yorinari Ochiai and Toshiro Iizuka designed the research study. Yorinari Ochiai wrote the paper. Yorinari Ochiai, Toshiro Iizuka, and Yoshio Hoshihara reviewed endoscopic findings. Yugo Suzuki, Junnosuke Hayasaka, Kosuke Nomura, Masami Tanaka, Hiroyuki Odagiri, Satoshi Yamashita, Akira Matsui, Daisuke Kikuchi, Masaki Ueno, Harushi Udagawa, and Shu Hoteya collected and analyzed the data.

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