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Original Article

Effect of Vonoprazan on Delayed Bleeding after Endoscopic Submucosal Dissection for Gastric Neoplasia among Antithrombotic Drug Users: A Single-Center, Single-Arm Prospective Observational Case Control Study

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Antithrombotic therapy is a major risk factor for delayed bleeding after endoscopic submucosal dissection (ESD) for gastric neoplasia. A potassium-competitive acid blocker, vonoprazan, is expected to prevent delayed bleeding better than conventional proton pomp inhibitors (PPIs), but the evidence is controversial. We sought to clarify the efficacy of vonoprazan for prevention of delayed bleeding after gastric ESD in patients under antithrombotic therapy. We prospectively registered 50 patients who underwent gastric ESD while receiving antithrombotic therapy and vonoprazan in our institution between October 2017 and September 2018. The incidence of delayed bleeding was compared with that in a historical control group of 116 patients treated with conventional PPI. We also evaluated risk factors associated with delayed bleeding. Delayed bleeding was observed in 8 of 50 patients (16.0%), which was not dissimilar from the incidence in the historical control group (12.1%) ($p = 0.49$). In the univariate analysis, age (> 70 years) ($p = 0.034$), multiple antithrombotic drug use ($p < 0.01$), procedure time (> 200 min) ($p = 0.038$) and tumor size (> 40 mm) ($p < 0.01$) were associated with delayed bleeding after gastric ESD, but vonoprazan was not ($p = 0.49$). Vonoprazan may not be more effective than conventional PPIs in preventing delayed bleeding after gastric ESD in patients receiving antithrombotic therapy.

Key words: vonoprazan, endoscopic submucosal dissection, antithrombotic drug, gastric cancer

Endoscopic submucosal dissection (ESD) is an accepted, minimally invasive treatment for early gastric cancer [1,2]. Delayed bleeding is reported to be the most frequent adverse event of gastric ESD, occurring in 4-5% of patients [3,4]. Although risk factors such as tumor size, location, and procedure time have been associated with delayed bleeding [5-7], use of antithrombotic drugs may be a more important risk factor [6-9]; the reported bleeding rate in users of multiple antithrombotic drugs is 14-35% [10,11]. Proton pomp inhibitors (PPIs) are commonly used in attempts to heal the artifactual gastric ulcer caused by ESD and to prevent delayed bleeding after the procedure. The efficacy of PPIs for post-ESD delayed bleeding has been reported [11,12]. It has been expected that vonoprazan, a new, novel potassium-competitive acid blocker, would be more effective than conventional PPIs in preventing delayed bleeding after gastric ESD because of its more

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rapid, potent, and sustained acid inhibition, but the results of the relevant studies have been conflicting [13, 14]. Therefore, we conducted a prospective observational case control study to evaluate the efficacy of vonoprazan for prevention of delayed bleeding in gastric ESD among patients receiving antithrombotic therapy.

Patients and Methods

Patients. Patients who were taking at least one antithrombotic drug and treated with gastric ESD at Kurashiki Central Hospital between October 2017 and September 2018 were prospectively enrolled in this study. Inclusion criteria were as follows: patients > 20 years old, having lesions indicated for ESD based on endoscopic and pathological findings, and taking antithrombotic agents which could be managed according to the guidelines proposed by the Japan Gastroenterological Endoscopy Society in 2012 and 2017 [15, 16]. Patients with perforation during ESD or patients for whom the management of antithrombotic drugs appeared to deviate from the protocols in the 2 guidelines were excluded. Although most antithrombotic agents were resumed on the next day after ESD, it was the operator's decision when to resume the drugs according to the risk of thrombosis and bleeding in each patient. Written informed consent was obtained from all patients prior to treatment. The study protocol was approved by the Research Ethics Committee of our hospital and was registered in the University Hospital Medical Network Clinical Trial Registry (UMIN000029300).

Study protocol. Patients took vonoprazan 20 mg several hours before ESD and received an intravenous infusion of omeprazole 20 mg on the evening of the day of treatment. All patients underwent a second-look endoscopy on the day after ESD, and preventive hemostasis was performed according to the endoscopists' decision. Oral vonoprazan of 20 mg/day was started after second-look endoscopy and continued for 4 weeks. Four weeks after ESD, patients visited our outpatient clinic, where they were informed of the histopathology of the resected lesions and were queried about post-ESD adverse events.

As a historical control group, 116 patients who were receiving antithrombotic therapy and underwent gastric ESD between January 2014 and December 2016 were analyzed. The inclusion and exclusion criteria were the same as those for the vonoprazan group, and all patients who met the criteria were enrolled. All patients had been given an intravenous dose of 20 mg omeprazole twice on the day of and twice on the day after ESD. Oral administration of esomeprazole 20 mg/day was started on Day 3 after ESD and continued until 4 weeks after ESD.

Delayed bleeding was defined as hematemesis or melena requiring emergent upper endoscopy or a decrease of hemoglobin concentration of more than 2 g/dl from the pre-ESD value. The incidence of delayed bleeding was compared between the vonoprazan group and historical control group, and risk factors associated with delayed bleeding were evaluated. When multiple lesions were consecutively resected, the total size of the lesions and total time for resection were used for the analysis.

Endoscopic procedures. Gastric ESD was performed with these instruments: 1) a regular video endoscope (GIF-Q260J; Olympus, Tokyo) and multibending endoscope (GIF-2TQ260M; Olympus); 2) an IT2 knife (KD-611L; Olympus), an IT nano knife (KD-612L; Olympus) or a Dual Knife (KD-650L; Olympus); and 3) a VIO 300D electrosurgical unit (ERBE, Tubingen, Germany).

Statistical analysis. The JMP version 14.0 software package (SAS Institute, Cary, NC, USA) was used for all statistical analyses. Continuous variables were expressed as the median and range and assessed by Student's *t*-test or nonparametric tests. Pearson's chi-squared test or Fisher's exact test was performed to compare categorical variables. Differences were considered significant at a p-value of less than 0.05.

Results

Patient characteristics. Baseline characteristics of patients are listed in Table 1. There were no significant differences between patients in the vonoprazan group and those in the control group with respect to age, rates of cardiovascular disease, history of smoking, renal failure, hemodialysis, liver cirrhosis, and diabetes mellitus, but significantly fewer patients in the control group were male and had hypertension.

Characteristics of the gastric lesions are listed in Table 2. Tumors in the vonoprazan group were larger than those in the control group ($p = 0.033$), but there were no significant differences between the 2 groups in terms of the location of the tumors in the stomach,

morphology and histopathology of the lesions, rates of en bloc resection, preventive hemostasis at second-look endoscopy, rates of R0 resection, or experience of the endoscopists.

Characteristics and management of antithrombotic agents. The patterns of use of antithrombotic agents are listed in Table 3. Single antiplatelet drug use was marginally more common in the vonoprazan group than in the control group ($p=0.05$). Fewer patients were treated with heparin replacement in the vonoprazan group than in the control group, but the number of patients who received heparin replacement was low,

Table 1 Characteristics of patients

	Vonoprazan group	Historical control	*p* value
Number of patients	50	116	
Age, median (range), years	78 (54–87)	75 (59–87)	0.078
Sex/male (%)	33 (66.0%)	100 (86.2%)	0.0038
History of smoking (%)	23 (46%)	63 (54.3%)	0.33
Cardiovascular disease (%)	29 (58.0%)	70 (60.3%)	0.78
*Renal failure (%)	23 (46%)	42 (36%)	0.24
Hemodialysis (%)	1 (2%)	4 (3.5%)	0.62
Liver cirrhosis (%)	0 (0%)	1 (0.8%)	0.39
Hypertension (%)	24 (48.0%)	81 (69.8%)	0.0074
Diabetes mellitus (%)	10 (20%)	40 (34.5%)	0.062

*Renal failure: eGFR <60 mL/min

Table 2 Characteristics of the lesions

	Vonoprazan	Historical control	*p* value
Tumor located in the antrum, (%)	13 (7.8)	37 (22.3)	0.44
Morphology/elevated type: 0-Ⅰ or Ⅱa, (%)	18 (36.0%)	56 (48.3%)	0.14
Tumor size (mm), median (range)	45 (15–90)	37 (18–104)	0.033
Tumor with ulcer, (%)	2 (4.0%)	6 (5.2%)	0.74
Pathological findings/Adenoma or Differentiated type, (%)	47 (95.9%)	115 (99.1%)	0.15
Tumor depth/Mucosal layer, (%)	47 (95.9%)	104 (89.7%)	0.19
En bloc resection, (%)	50 (100%)	113 (97.4%)	0.25
Procedure time, median (range)	107 (30–326)	101 (27–383)	0.96
Preventive hemostasis at second-look endoscopy, (%)	29 (58.0%)	77 (66.4%)	0.30
R0 resection, (%)	46 (92.0%)	107 (92.2%)	0.96
Experience of endoscopist >6 years, (%)	26 (52.0%)	51 (44.0%)	0.34

Table 3 Characteristics of the antithrombotic drugs

	Vonoprazan (n=50)	Historical control (n=116)	*p* value
Single antiplatelet drug user	34 (68.0%)	60 (51.7%)	0.05
Single anticoagulant drug user	8 (16.0%)	28 (24.1%)	0.24
Multiple antithrombotic drugs user	8 (16.0%)	28 (24.1%)	0.24
Single aspirin user	18 (34.0%)	36 (31.0%)	0.71
Single thienopyridine user	5 (8.0%)	15 (12.9%)	0.35
Dual antiplatelet therapy	5 (10.0%)	22 (19.0%)	0.15
DOAC	9 (18.0%)	17 (14.7%)	0.59
Warfarin	3 (6.0%)	18 (15.5%)	0.09
Heparin replacement	2 (4.0%)	17 (14.7%)	0.048
Warfarin continue	1 (2%)	1 (0.86%)	0.50

DOAC, direct oral anticoagulant.

and the difference was marginal ($p=0.048$); the difference may have been due to changes made by the Japan Gastroenterological Endoscopy Society in 2017 to the guidelines for endoscopy in patients undergoing antithrombotic treatment [15]. The management of antithrombotic drugs is summarized in Table 4. In the vonoprazan group, direct oral anticoagulants (DOAC) were more frequently discontinued according to the 2017 guidelines and restarted on the next morning than in the historical control group ($p<0.01$). Antiplatelet drugs were mostly discontinued following the 2012 guidelines in both groups, but were restarted significantly earlier in the vonoprazan group than in the control group ($p=0.012$). Additionally, any antithrombotic drugs were restarted significantly earlier in the vonoprazan group ($p<0.01$).

Outcomes. Delayed bleeding was observed in 8 of 50 patients treated with vonoprazan (16.0%, 95% confidence interval 8.3-28.5%), which was not significantly different from the percentage of incidence in the historical group (12.1%, 7.3-19.2%) ($p=0.49$) (Table 5). The incidence of delayed bleeding in patients with single anticoagulant treatment tended to be higher in the vonoprazan group (25%, 2/8) than the control group (3.6%, 1/28) ($p=0.05$), but the number of patients treated was low. Earlier resumption of any antithrombotic drugs was not significantly associated with a difference in delayed bleeding between the 2 groups. All delayed bleeding was successfully managed with endoscopic hemostasis, and none of the patients needed

Table 4 Management of the antithrombotic drugs

	Vonoprazan (n=50)	Historical control (n=116)	*p* value
Cessation of DOAC			
*following the 2017 guidelines	7/ 9 (77.8%)	1/ 17 (5.9%)	0.0004
Cessation of any antiplatelet drug			
**following the 2012 guidelines	38/42 (90.5%)	72/ 88 (81.8%)	0.29
Resumption of DOAC			
continue or restart until the following day	8/ 9 (88.9%)	3/ 17 (17.6%)	0.0008
Resumption of any antiplatelet drug			
continue or restart until the following day	33/42 (78.6%)	49/ 88 (55.7%)	0.012
Resumption of any antithrombotic drugs			
continue or restart until the following day	44/50 (88%)	57/116 (49.1%)	<0.0001

*The Japanese Gastroenterological Endoscopy Society revised the guidelines in 2017 (see the 2017 appendix).
**The Japanese Gastroenterological Endoscopy Society revised the guidelines in 2012.

Table 5 Incidence of delayed bleeding

	Vonoprazan group	Historical control	*p* value
Delayed bleeding	8/50 (16.0%: 95%CI 8.3–28.5%)	14/116 (12.1%: 95%CI 7.3–19.2%)	0.49
Single antiplatelet drug user	4/34 (11.8%)	4/60 (6.7%)	0.39
Single anticoagulant drug user	2/ 8 (25.0%)	1/28 (3.6%)	0.05
Multiple antithrombotic drugs user	2/ 8 (25.0%)	9/28 (32.1%)	0.70
Single aspirin user	2/18 (11.1%)	3/36 (8.3%)	0.75
Single thienopyridine user	0/ 5 (0%)	1/15 (6.7%)	0.44
Single another antiplatelet user	2/11 (18.2%)	0/ 9 (0%)	0.49
Dual antiplatelet therapy	2/ 5 (40.0%)	7/22 (31.2%)	0.73
DOAC	1/ 9 (11.1%)	1/17 (5.9%)	0.63
Heparin replacement	1/ 2 (50.0%)	3/17 (17.6%)	0.26
Resumption of any antithrombotic drugs continue or restart until the following day	6/44 (13.6%)	7/57 (12.3%)	1.00

blood transfusion. No adverse events other than delayed bleeding, including thromboembolic events, were recorded in the study population.

Risk factors for delayed bleeding. In the univariate analysis, age (>70 years) (odds ratio 0.35, 95% confidence interval 0.13-0.95, $p=0.034$), multiple antithrombotic drug use (odds ratio 4.76, 1.86-12.2, $p<0.01$), procedure time (>200 min) (3.24, 1.02-10.3, $p=0.038$) and tumor size (>40 mm) (4.25, 1.49-12.1, $p<0.01$) were associated with delayed bleeding after gastric ESD, but vonoprazan use was not (1.38, 0.54-3.55, $p=0.49$) (Table 6).

Discussion

In this prospective study, the incidence of delayed bleeding after gastric ESD treated by vonoprazan was 16% in patients under antithrombotic therapy, which was not significantly different from that in patients treated with conventional PPIs (12.1%). Two previously reported prospective studies on the prevention pf delayed bleeding after gastric ESD have yielded conflicting results [13,14]. Hamada *et al.* [13] reported that delayed bleeding occurred in 4.3% of vonoprazan-treated patients and in 5.7% of patients treated with conventional PPIs, an insignificant difference. In contrast, Kagawa *et al.* [14] reported that vonoprazan-treated patients had a significantly lower incidence of delayed bleeding than did a historical group of patients treated with conventional PPIs (1.3%, 1/75 patients vs. 10.0%, 15/150 patients); even in the subgroup of patients receiving antithrombotic therapy, the incidence of bleeding in patients treated with vonoprazan (0%, 0/15) was significantly lower than that in patients treated with conventional PPIs (25%, 6/24) [14]. In their study, however, the incidence of delayed bleeding in the historical PPI group was higher than those in the earlier reports [3,4,11] and that in the present study.

In previous studies [6-9], multiple antithrombotic drug use and tumor size were identified as independent risk factors associated with delayed bleeding after gastric ESD. Vonoprazan was more effective than lansoprazole in preventing bleeding from low-dose aspirin-induced ulcers, especially in patients receiving additional antithrombotic drugs [17]. Thus, we expected to observe a lower rate of delayed bleeding after gastric ESD in the vonoprazan group than the conventional PPI-treated group, but this was not the case; the incidence of delayed bleeding was similar between the vonoprazan and conventional PPI groups, even in patients receiving multiple antithrombotic drugs.

There were several limitations of our study. First, we compared the incidence of bleeding of the vonoprazan group with that of a historical control group. In 2017, the Japanese Gastroenterological Endoscopy Society revised the guidelines (2017 appendix) [15,16] for the management of antithrombotic agents during endoscopic procedures with bleeding risk, taking the risk of thromboembolic events due to drug cessation into account rather than bleeding risk. Thus, the differences in the management of antithrombotic drugs between the

Table 6 Risk factors associated with delayed bleeding

	Univariate analysis	
Variable	Odds ratio (95% CI)	*p* value
Vonoprazan	1.38 (0.54–3.55)	0.49
Age >70	0.35 (0.13–0.95)	0.034
Sex: male	2.74 (0.61–12.4)	0.25
Multiple antithrombotic drugs user	4.76 (1.86–12.2)	0.0005
Procedure time >200 min	3.24 (1.02–10.3)	0.038
Tumor size >40 mm	4.25 (1.49–12.1)	0.0041
Cardiovascular disease	1.21 (0.48–3.08)	0.68
Heparin bridge	1.91 (0.57–6.40)	0.29
Renal failure	1.35 (0.55–3.33)	0.64
Hypertension	1.02 (0.40–2.59)	0.97
History of smoking	1.40 (0.57–3.49)	0.54
Resumption of any antithrombotics continue or restart until the following day	1.12 (0.35–3.6)	0.84

groups could have influenced the results. In fact, more patients in the vonoprazan group were treated with shorter interruption of DOAC or any antithrombotic agents, but the early resumption of antithrombotic agents was not associated with ESD-related bleeding risk. Second, the number of subjects in this study may not have been large enough to reveal a difference in the effect of vonoprazan vs. conventional PPIs on the delayed bleeding. There had been no report on the risk of delayed bleeding after ESD in patients receiving antithrombotics therapy with vonoprazan when we planned this prospective study. Therefore, the sample size decision was difficult, and in the end we elected to conduct this research as a pilot study with a historical control. As a result, the number of cases with delayed bleeding was insufficient to perform a multivariate logistic regression analysis. However, our pilot study is expected to lead to further large-scale prospective studies. Third, we should consider the selection bias of patients in the historical control group. To reduce this bias, we included all cases who satisfied the inclusion criteria during the study period. Thus, we could not adjust the background characteristics between the 2 groups.

In conclusion, the incidence of delayed bleeding after gastric ESD in patients receiving antithrombotic therapy was not different between patients treated with vonorozan and those treated with conventional PPIs. To further assess the putative effectiveness of vonoprazan in the prevention of bleeding after ESD of gastric lesions in patients receiving antithrombotic therapy, large-scale, prospective studies should be conducted.

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