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Risk Factors for Delayed Ulcer Healing after Endoscopic Submucosal Dissection of Gastric Neoplasms

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ABSTRACT

Background & Aims: With improved technology, the size of artificial ulcers after endoscopic submucosal dissection (ESD) has increased. The aim of our study was to examine the risk factors for delayed gastric ulcer healing after ESD, including the possible benefit of potassium-competitive acid blocker (P-CAB) treatment.
Methods: The primary outcome was the rate of healing of the artificial ulcers induced by ESD at 8 weeks post intervention. Design: retrospective case series. Setting: Aichi Medical University Hospital. Patients: patients who underwent ESD for gastric neoplasm, between April 2015 and March 2017. Intervention: ESD, with a follow-up endoscopic examination at 8 weeks post-ESD. Univariate and multivariate analyses were used to identify the independent risk factors for delayed healing.
Results: Of the 73 gastric neoplasms included in the analysis, delayed ulcer healing was identified in 21.9%. Dyslipidemia (p=0.04), ESD procedure time (p=0.003) and artificial ulcer size (p<0.001) were identified as risk factors for delayed healing, with location in the lower third of the stomach [Odds ratio (OR) 6.76; p=0.016] and artificial ulcer size (OR, 1.18; p=0.024) retained as independent risk factors. A cut-off ulcer size of 854 mm^2 was predictive of delayed healing, with a sensitivity of 29.8% and specificity of 87.5%. For large ulcers, the rate of healing of 70% with vonoprazan was higher than the rate of 47.6% with proton pump inhibitors (PPIs), although this difference was not significant.
Conclusion: For artificial ulcers after ESD with a resection diameter >35 mm, it might be desirable to use PPIs for >8 weeks or P-CAB.

Key words: endoscopic submucosal dissection – artificial ulcer – healing – potassium-competitive acid blocker – proton pump inhibitor.

Abbreviations: EGC: early gastric cancers; EMR: endoscopic mucosal resection; ESD: endoscopic submucosal dissection; *H. pylori: Helicobacter pylori*; H2RA: H2-receptor antagonist: PRP: platelet rich plasma; PGA: polyglycolic acid; P-CAB: potassium-competitive acid blocker; PPI: proton pump inhibitor.

INTRODUCTION

Endoscopic submucosal dissection (ESD) is considered to be the standard treatment for the resection of gastric neoplasm, instead of endoscopic mucosal resection (EMR), as it allows en-bloc resection of the lesion. However, with the technical improvements in the ESD procedure that permit a wider and deeper area of resection, the risk for the development of an artificial ulcer after ESD has increased. Compared to the peptic ulcers, EMR-induced ulcers tend to heal faster and to have a lower rate of relapse. The better healing of EMR-induced ulcers than that of peptic ulcers is due to the preservation of the contractility of the muscularis propria layer, which is usually damaged in the case of peptic ulcers [1]. The healing of EMR-induced ulcers might be facilitated by the increased blood supply at the margins of the ulcer, resulting from increased levels of nitric oxide, epidermal growth factor and endogenous prostaglandin [2]. However, delayed ulcer healing of >8 weeks has been reported in 5–20% of patients following ESD [3, 4].

Acid-suppressing agents are consistently administered to induce rapid healing of artificial gastric ulcers, with some studies having reported proton pump inhibitors (PPI) to be more effective than histamine H2-receptor antagonists (H2RA) in promoting the healing of post-ESD ulcers [5, 6]. A potassium-competitive acid blocker (P-CAB), which has a stronger antacid

effect than conventional PPIs, was released for clinical use in Japan in February 2015. Among these P-CABs, the antacid effect of vonoprazan has specifically been reported as being more potent than PPIs [7], resulting in greater effectiveness for the treatment of acid-related diseases, such as gastroesophageal reflux disease or *Helicobacter pylori* (*H. pylori*) eradication. Therefore, vonoprazan could be more effective for the management of artificial ulcers after ESD, compared to conventional PPIs, which are currently considered to be the gold standard treatment for the management of post-ESD ulcers. The effectiveness of vonoprazan for the treatment of post-ESD ulcers has not been systematically evaluated and there is no clinical consensus regarding potential advantages of vonoprazan treatment compared to PPIs. Moreover, PPI treatment for artificial ulcers induced by ESD is usually continued for 4-8 weeks [1, 2, 8]. However, there is no current consensus regarding the optimal duration of PPI or P-CAB treatment after ESD based on the various factors that can influence healing of post-ESD ulcers. Potential predictive factors of delayed ulcer healing include the large size of artificial ulcers [9, 10], the use of H2RA after ESD [5, 6], preoperative fibrosis in the submucosal layer of the lesions [3], damage to the muscularis propria layer during the ESD procedure [11], location of the resected lesion in the lesser curvature [12], and lesions combined with severe atrophic gastritis [13]. However, these risk factors were identified prior to the release of P-CABs and, therefore, these studies did not consider P-CAB treatment.

The aim of our study was to examine the risk factors associated with delayed ulcer healing after ESD among patients treated with P-CAB, and to determine the optimal antacid treatment for artificial ulcers after ESD.

METHODS

Patients

We enrolled patients who had undergone ESD for gastric lesions, including early gastric cancer (EGC) and adenoma, at the Aichi Medical University Hospital, between April 2015 and March 2017. Endoscopic submucosal dissection was indicated when the following criteria were met: any lesions with adenoma, regardless of size; well-to-moderately differentiated adenocarcinoma confined to the mucosa, with a diameter <2 cm; well-to-moderately differentiated adenocarcinoma, with a diameter >2 cm and without ulcer finding [UL (-)]; well-to-moderately differentiated adenocarcinoma, with a diameter <3 cm and UL (+); poorly differentiated adenocarcinoma <2 cm and UL (-), without evidence of lymph node invasion or distant metastases on abdominal computed tomography or endoscopic ultrasonography. Of note, according to the pathological results obtained after ESD, some patients with non-curative lesions were initially treated with ESD. In these cases, the decision to perform additional surgery was based on the treating physician's recommendation and the patient's decision. Patients who did not undergo follow-up endoscopic examination at 8-weeks post-treatment and those who underwent additional surgery after ESD were excluded from the analysis.

Procedures

We carried out ESD for gastric lesions with either a conventional single-channel endoscope (GIF-H260Z, GIF-Q260J or GIF-HQ290; Olympus Corp. Tokyo, Japan) or a multi-bending two channel endoscope (GIF-2TQ260M; Olympus Corp. Tokyo, Japan). The injection solutions contained glycerin and hyaluronic acid sodium (0.4%), with 1% indigocarmine dye. Solutions were injected locally into the submucosal layer using a disposable 25-gauge needle (Top Corp. Tokyo, Japan). As a cutting device, the Dualknife (KD-650L; Olympus Corp. Tokyo, Japan) was primarily used, with the FlushKnife BT knife (DK2618JB; Fujifilm Corp. Tokyo, Japan), IT Knife2 (KD-611L; Olympus Corp. Tokyo, Japan) or CluchCutter (DP2618DT; Fujifilm Corp. Tokyo, Japan) being used on occasion. An electrosurgical current was applied with the use of an electrosurgical generator (VIO300D; Erbe Elektromedizin GmbH. Tuebingen, Germany). Ulcers that developed after ESD were carefully examined endoscopically and any visible vessels were heat-coagulated using a Coagrasper (FD410LR; Olympus Corp. Tokyo, Japan). The maximal diameter of the ESD-induced artificial ulcer and the diameter perpendicular to the maximum diameter were measured using a bendable endoscopic measuring device (M2-3U; Olympus Corp. Tokyo, Japan). The area of the ulcers was calculated based on the assumption of an elliptical shape.

A PPI (lansoprazole 30 mg/day) was administered intravenously to all patients post-ESD and on post-ESD day 1. Subsequently, daily oral doses of PPI (esomeprazole 20 mg/day, lansoprazole 30 mg/day, omeprazole 20 mg/day, or rabeprazole 10 mg/day) or P-CAB (vonoprazan 10 mg/day) were prescribed for 8 weeks. The oral feeding was permitted on post-ESD day 2, and the patients were discharged on post-ESD day 4 to 6, with instructions to call the hospital and visit the emergency department immediately in case of overt bleeding. Delayed bleeding was defined as hematemesis or melena that required endoscopic hemostasis, or as a decrease in the hemoglobin level >2.0 g/dL compared to the most recent preprocedural level or the level obtained within 2 days after ESD. Bleeding that occurred during the ESD procedure was not included in our definition of delayed bleeding. About two weeks post-ESD, all patients returned to our outpatient department to receive the final pathology report. At that time, any event of delayed bleeding and the necessity for further surgical resection was clinically assessed. When no further surgery was deemed to be necessary, a follow-up endoscopy was scheduled at 8 weeks, and annually thereafter.

Data analysis

The primary outcome of our study was the rate of healing of the artificial ESD-induced ulcer at 8-weeks post-intervention. The secondary outcome was the prevalence rate of delayed ulcer healing. To search for potential risk factors of delayed ulcer healing, the following factors were analyzed: age, sex, co-morbidities that may affect mucosal healing (hypertension, dyslipidemia, diabetes mellitus, myocardial infarction, cerebral infarction, liver cirrhosis, and kidney disease), use of antiplatelet or nonsteroidal anti-inflammatory drugs, *H. pylori* infection, history of *H. pylori* eradication, type of antacids after ESD (PPI or P-CAB), location of the lesion (upper / middle third or lower third of the stomach, anterior wall or posterior wall), pathological diagnosis of the lesion (adenoma or EGC), ESD procedure time, artificial ulcer size, the number

of intraoperative bleeding occurrences, and the occurrence of delayed bleeding.

For univariate analysis, categorical variables were analyzed using Fisher's exact test or Man-Whitney U test. Variables with a p value <0.20 in univariate analyses were entered into a multivariate stepwise logistic regression analysis, using a p value <0.10 for entry. A p value <0.05 was considered significant. All analyses were performed using BellCurve for Excel (Social Survey Research Information Co. Japan).

RESULTS

A total of 81 gastric neoplasms were resected using ESD. Among these, 6 were excluded based on the absence of a follow-up endoscopic examination at 8 weeks, and 2 others which required additional surgery. Therefore, 73 neoplasms were entered into the final analysis, including 23 adenomas and 50 EGCs (Flow diagram, Fig. 1). The relevant demographic and clinical characteristics of our study group are summarized in Table I.

Table I. Baseline demographic and clinical characteristics.

	Overall (n=73)
Age, median (range), years	73 (66 - 77)
Sex, n (Male : Female)	(57 : 16)
Co-morbidity, n (%)	
Hypertension	45 (61.6)
Dyslipidemia	28 (38.3)
Diabetes mellitus	16 (21.9)
Myocardial infarction	8 (11.0)
Cerebral infarction	2 (2.7)
Liver cirrhosis	3 (4.1)
Kidney disease	2 (2.7)
Medication, n (%)	
NSAID	14 (19.2)
Antiplatelet	5 (6.8)
H. pylori infection, n (%)	9 (12.3)
H. pylori eradication history, n (%)	24 (32.9)

NSAID: non-steroidal anti-inflammatory drug

Table II. Tumor and ESD-related characteristics.

	Overall (n=73)
Diagnosis, n (%)	
Cancer	50 (68.5)
Adenoma	23 (31.5)
Location, n	
Upper / middle third: Lower third	22:51
Anterior wall: Posterior wall	27:46
Procedure time, median (range), min	130 (90 - 195)
Artificial ulcer size, median (range), mm^2	667 (471 - 1300)
Occurrence of delayed bleeding, n (%)	3 (4.1)

Tumor and ESD-related characteristics

Among the total lesions resected by ESD, 23 (31.5%) were adenomas and 50 (68.5%) were EGC (Table II). Twenty-two were localized in the upper or middle third of the stomach and 27 were on the anterior wall.

Overall, the mean ESD procedure time was 130 min and the mean artificial ulcer size after ESD was 667 mm^2. With regard to the rate of ulcer healing, among the 73 patients in our study group, 16 presented with an unhealed ulcer at the 8-week follow up. In all of these 16 patients, ulcers were in the healing stage at the time of the follow-up endoscopic examination (Table II). Occurrence of delayed bleeding was reported in 3 cases, with 2 of these patients completing the follow-up endoscopic examination at 8 weeks.

Risk factors for delayed ulcer healing after ESD

On univariate analysis, dyslipidemia (p=0.04), ESD procedure time (p=0.003) and artificial ulcer size (p< 0.001) were identified as risk factors of delayed ulcer healing. The type of antisecretory used was not identified as a risk factor. The following factors had a p value of <0.20: dyslipidemia,

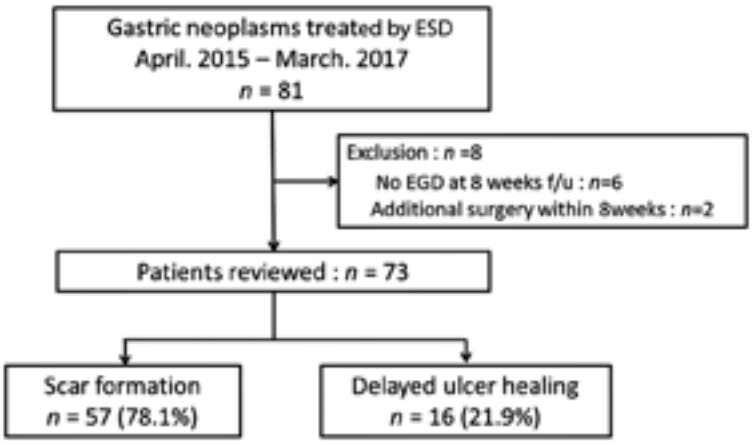

Fig. 1. Flow chart of the patients included in the study. Of the 81 eligible patients, 8 were excluded. After exclusion of these cases, 57 patients were included in the scar formation group and 16 patients in the delayed ulcer healing group. ESD, endoscopic submucosal dissection; EGD, esophagogastroduodenoscopy.

Table III. Univariate analysis for delayed post-ESD ulcer healing.

	Scar formation group (n=57)	Delayed ulcer healing group (n=16)	p value
Age, median (range), years	73 (67 - 77)	71.5 (64 - 76)	0.459
Sex, n (Male: Female)	(45:12)	(12:4)	0.740
Co-morbidity, n (%)			
Hypertension	36 (63.3)	9(56.3)	0.770
Dyslipidemia	18 (31.6)	10 (62.5)	0.040*
Diabetes mellitus	11 (19.3)	5 (31.3)	0.321
Myocardial infarction	5 (8.8)	3 (18.8)	0.361
Cerebral infarction	2 (3.5)	0 (0.0)	NA
Liver cirrhosis	3 (5.3)	0 (0.0)	NA
Kidney disease	1 (1.8)	1 (6.3)	0.390
Medication, n (%)			
NSAID	10 (17.5)	4 (25.0)	0.491
Antiplatelet	4 (7.0)	1 (6.3)	1.000
H. pylori infection, n (%)	8 (14.0)	1 (6.3)	0.673
H. pylori eradication history, n (%)	20 (35.0)	4 (25.0)	0.555
Antacid, n (PPI:P-CAB)	(34:23)	(12:4)	0.381
Location, n			
Upper / middle third: Lower third	20:37	2:14	0.075
Anterior wall: Posterior wall	21:36	6:10	1.000
Pathology, n (adenoma: cancer)	(20:37)	(3:13)	0.361
Operative time, median (range), min	118 (82 - 178)	195 (147.5 - 242.5)	0.003*
Artificial ulcer size, median (range), mm^2	612 (392.5 - 942)	1440 (932.5 - 1884)	<0.001*
Number of occurrences of intraoperative bleeding, median (range)	3 (1 - 6)	3.5 (1.5 - 5.5)	0.595
Occurrence of delayed bleeding, n (%)	3 (5.3)	0 (0.0)	NA

NSAID: non-steroidal anti-inflammatory drug; NA: not applicable; *p<0.05

location (upper / middle third and lower third of the stomach), procedure time, and artificial ulcer size (Table III). These factors, in addition to age and sex, were entered into the multivariate analysis, with the following being identified as independent risk factors of delayed ulcer healing; location in the lower third of the stomach and artificial ulcer size; dyslipidemia and procedure time were not retained as independent risk factors (Table IV).

Table IV. Multivariate analysis for delayed post-ESD ulcer healing.

	OR	95% CI	p value
Sex	3.59	0.62 - 20.73	0.154
Dyslipidemia	4.05	0.97 - 16.98	0.056
Location (lower third)	6.76	1.03 - 44.52	0.016*
Procedure time	1.09	0.98 - 1.20	0.095
Artificial ulcer size	1.18	1.02 - 1.36	0.024*

OR: Odds ratio; CI: confidence interva; *p<0.05

On the ROC curve analysis, a cut-off ulcer size of 854 mm^2 was predictive of delayed ulcer healing, with a sensitivity of 29.8% and specificity of 87.5% (Fig. 2). The 854 mm^2 size is equivalent to a 35-mm diameter for an ulcer.

DISCUSSION

In our study group, the rate of delayed ulcer healing at 8 weeks post-ESD was 21.9%, which was slightly higher than the rate in previous reports [3, 4]. This might reflect our hospital's policy of allowing training endoscopists to perform the ESD procedure for educational purpose, which might increase the risk of damage to the muscularis propria layer during the procedure [11]. We found that large artificial ulcers and location of the lesion in the lower third of the gastric tract to be independent risk factors of delayed post-ESD ulcer healing. Our finding of delayed healing of large artificial ulcers is consistent with the results of Kobayashi et al. [9] and Oh et al. [10]. Size of artificial ulcer after ESD has also been reported to affect the healing rate of artificial ulcers in previous studies [9, 10, 14], supporting our findings.

After adjustment for other factors, lesions located in the lower third of the stomach were found to be predictive of delayed ulcer healing. Lim et al. [4] reported that lesions located in the middle third of the stomach were associated with delayed ulcer healing, although they did not adjust their predictive model for other associated factors. Of note, however, the high rate (70%) of lesions located in the lower third of the stomach might have influenced our results. The peristalsis in the lower third of the stomach is stronger than at other locations, which

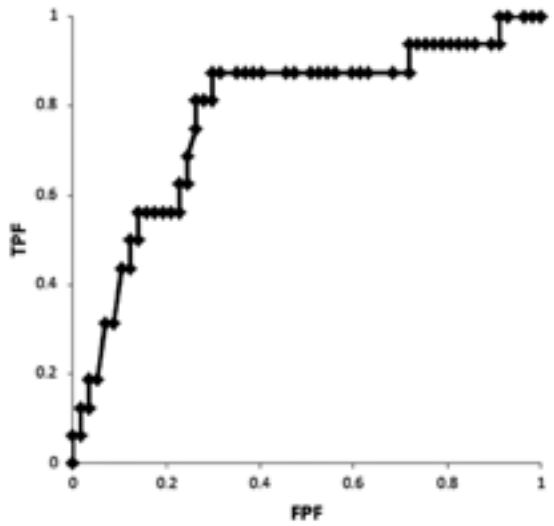

Fig. 2. The receiver operating characteristic (ROC) curve used to determine the optimal cut-off score of ulcer size to predict delayed healing. The cut-off value of 854 mm^2 provided a sensitivity of 29.8% and specificity of 87.5%. FPF, false positive fraction; TPR, true positive fraction.

might be one of the factors associated with delayed healing of ulcers in this location.

Vonoprazan is one of the new class of acid-suppressing agents that may be used as an alternative to PPIs as blocker of gastric hydrogen-potassium adenosine triphosphatase, which inhibits the critical final step in gastric acid secretion by reversing K+-competitive ionic binding. The pharmaceutical advantages of P-CAB over PPIs include more rapid, stronger and longer-lasting inhibition of gastric acid secretion after administration [7, 15, 16]. For the treatment of peptic ulcers, Miwa et al. reported that a 20 mg dose of vonoprazan had a similar tolerability profile as a 30 mg dose of lansoprazole, and was not inferior to lansoprazole with respect to gastric ulcer healing [17]. The relative effectiveness of vonoprazan compared to PPIs for the management of artificial ulcers after ESD remains controversial. Takahashi et al. [18] reported that the shrinking rates of ESD ulcers on day 8 and 28 were not statistically different between the vonoprazan 20 mg and lansoprazole 30 mg groups. On the other hand, Tsuchiya et al. [19] reported that vonoprazan significantly improved the healing rate in artificial ulcers, compared to the rate for esomeprazole. In the present study, the healing rate between PPIs and vonoprazan treatment was not different. This result might have been influenced by the comparatively lower number of cases included in our study than in the previous studies. Specifically among cases with an ulcer area >854 mm^2, the healing rate with vonoprazan was 70% (7/10), which was higher than the 47.6% (10/21) healing rate with PPI treatment. However, this difference was not significant. As the number of patients treated with vonoprazan accumulates, future analysis might reveal vonoprazan to be a superior treatment to the conventional PPIs.

On univariate analysis, we identified dyslipidemia as an independent risk factor for delayed ulcer healing after ESD. This finding has not been previously reported. Previous studies have reported diabetes mellitus to be a risk factor for delayed ulcer healing after ESD [4], with animal studies confirming delayed gastric ulcer healing in diabetic rats [20, 21]. As dyslipidemia was not retained as an independent risk factor on multivariate analysis, the size of the artificial ulcer might be a greater risk factor for delayed ulcer healing than specific factors in the patient's background.

H. pylori status was not found to have an effect on artificial ulcer healing. Previous studies have reported that *H. pylori* eradication therapy does not influence the rate of ulcer reduction after EMR [3, 22]. On the other hand, another study reported that *H. pylori* eradication therapy facilitated gastric ulcer healing after endoscopic resection [23]. Differences in these results were thought to be due to differences in the size of the artificial ulcer, with a larger influence of *H. pylori* status on smaller than larger ulcers after endoscopic resection.

Recently, endoscopic tissue shielding, which consists of using polyglycolic acid (PGA) sheets (Neoveil; Gunze Co, Kyoto, Japan) and fibrin glue (Beriplast P Combi-Set; CSL Behring Pharma, Tokyo, Japan), has been used for after gastric ESD. Tsuji et al. [24] and Fukuda et al. [25] reported that the combined use of PGA felt and fibrin glue offers promise as a method to prevent bleeding after ESD. Takimoto et al. [26] further reported the PGA felt and fibrin glue sealing method to be effective in treating large perforation and delayed perforations post-ESD. To our knowledge, however, there are no reports regarding the application of this sealing technique to promote ulcer healing after ESD. Such evidence would be useful for the treatment of large artificial ulcers or artificial ulcers in the lower third of the stomach. Shielding using platelet rich plasma (PRP) has also been shown to be effective in significantly reducing the size of EMR-induced ulcers of the colon in both rats and pigs (2.4% reduction in the control group versus 80% in treated animals) [27]. However, to our knowledge, there are no clinical reports on the use of PRP for the treatment of ulcers post-ESD.

A potential limitation of this study is the insufficient number of patients. Another possible limitation is the non-prospective and non-randomized study design. Further large-scale, multicenter and randomized studies may need to clarify the risk factors for delayed ulcer healing after ESD in patients treated with P-CABs, with the accumulation of evidence contributing to the development of guidelines to optimize patient care after ESD.

CONCLUSION

This is the first study which has investigated the risk factors for delayed artificial ulcer healing after vonoprazan was released for clinical use. We identified large artificial ulcers and lesions in the lower third of the stomach as independent risk factors for delayed healing. For artificial ulcers after ESD with a resection diameter >35 mm, it might be more desirable to use PPI for >8 weeks or to use vonoprazan.

Conflicts of interest: K.K. received research grants from the Research Organization for Daiich Sankyo Co., Ltd., Astra Zeneca Co., Ltd., EA Pharma Co., Ltd., and Takeda Pharmaceutical CO., Ltd. The other authors have no conflicts of interest to declare.

Author contributions: A.K., M.S., and K.K. designed the study. N.O., Y.F., M.E., Y.T., S.I., Y.H., and Y.Y collected data and carried out the study. A.K. and M.S analyzed the data. All authors contributed to the writing and approved the manuscript.

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