Journal of Rural Medicine

Original article

Feasibility of gastric endoscopic submucosal dissection without using proton pump inhibitor injection: a propensity score analysis

Saki Fushimi[1], Yohei Horikawa[1], Hiroya Mizutamari[1], Nobuya Mimori[1], Yuhei Kato[1], and Sayaka Sato[1]

[1]*Department of Gastroenterology, Hiraka General Hospital, Japan*

Abstract

Purpose: Endoscopic submucosal dissection is a promising method for the resection of superficial gastric neoplasms. To date, several institutions have used proton pump inhibitor injections over the perioperative period. However, there is very little evidence regarding their efficacy. To overcome this limitation, we compared procedural outcomes and the prevention of adverse events of proton pump inhibitor injection with an orally administered active potassium-competitive acid blocker alone.

Participants and Methods: We enrolled a total of 150 patients treated for superficial gastric neoplasms at a single institution between April 2015 and December 2018. Patients treated for 2 days with proton pump inhibitor injections following 12 days of oral potassium-competitive acid blocker (proton pump inhibitor group=80) were compared with patients treated for 14 days orally with potassium-competitive acid blocker alone (potassium-competitive acid blocker group=70) using propensity score analysis. We evaluated intragastric pH levels prior to endoscopic submucosal dissection, frequency of intraoperative major bleeding, procedure time, *en bloc* resection rate, curability, ulcer reduction rate 14 days after endoscopic submucosal dissection, and adverse events (including perforation and postoperative bleeding).

Results: Propensity score analysis yielded 43 matched pairs. The comparison demonstrated similar values for the outcomes. For all cases, we observed intragastric pH levels >6.4 prior to endoscopic submucosal dissection. Postoperative bleeding rates were 2.3% (1/43) in the proton pump inhibitor group and 0.0% (0/43) in the potassium-competitive acid blocker group (P=0.315).

Conclusions: Oral potassium-competitive acid blocker alone was as effective as proton pump inhibitor injection, with a low incidence of adverse events. Based on these results, proton pump inhibitor injection might be omitted during gastric endoscopic submucosal dissection.

Key words: proton pump inhibitors injection, potassium-competitive acid blocker, ulcer healing, gastric endoscopic submucosal dissection

(J Rural Med 2020; 15(3): 85–91)

Introduction

Endoscopic submucosal dissection (ESD) is a promising method for the resection of superficial gastric neoplasms[1–4].

Received: December 23, 2019
Accepted: February 20, 2020
Correspondence: Yohei Horikawa, Department of Gastroenterology, Hiraka General Hospital, 3-1 Yatukuchi, Maego, Yokote-shi, Akita 013-8610, Japan
E-mail: horikawa_01@me.com

Historically, proton pump inhibitor (PPI) injection has been used in the perioperative period of ESDs based on peptic ulcer treatment. However, to date, there has been little evidence as to the efficacy of PPI injection in this period[5].

Vonoprazan is an orally administered active potassium-competitive acid blocker (P-CAB). It has been considered a potential alternative to PPIs for the treatment of acid-related diseases[6]. Recently, several studies have investigated the efficacy of vonoprazan in gastric ESD-derived ulcers[7–11]. Importantly, as compared with PPI therapy, P-CAB therapy achieved comparable or superior efficacy in ulcer healing. To date, the utility of vonoprazan for gastric ESD has not been completely established. However, compared with the commonly used PPIs, the effects of vonoprazan can be expected to suppress acid secretion and rapidly increase gas-

tric pH compared with PPIs.

The most serious adverse event in ESD is postoperative bleeding, which can take place within the first two weeks[12–14]. Specifically, the incidence of postoperative bleeding has been reported to be around 4.5%[15]. However, artificial ulcers induced by ESD are treated with PPIs for 4–8 weeks, according to the peptic ulcer therapy protocol.

Therefore, in the present study, we evaluated the improvement of procedure outcomes and the prevention of adverse events including postoperative bleeding in patients treated with PPI injection followed by P-CAB administration or P-CAB administration alone. Data were evaluated using propensity score matching (PSM) analysis[16].

Methods

Participants

We enrolled a total of 270 consecutive patients with superficial gastric neoplasms. Individuals were treated by ESD at the Hiraka General Hospital between April 2015 and December 2018. Data were collected from the hospital database and retrospectively reviewed. Patients included in the study were those who underwent gastric ESD in our institution for cancers adhering to the absolute and expanded criteria[17, 18] established by endoscopy. Exclusion criteria were as follows: history of prior surgery (n=4), antithrombotic therapy (n=49), prior use of acid suppressant (n=20), and other acid suppressants for ESD (n=47). Finally, a total of 150 patients were included. Patients were intravenously infused with omeprazole (20 mg b.i.d.) for the first two days following the oral administration of 20 mg of vonoprazan for 12 days (PPI group; n=80), who were treated between April 2015 and December 2016. Alternatively, patients were administered 20 mg vonoprazan alone for 14 days (P-CAB group; n=70), who were treated between January 2017 and December 2018 (Figure 1). *Helicobacter pylori* (*H. pylori*) infection was assessed in all patients by at least one of the following three methods: (1) the anti-*Hp* immunoglobulin G serological test, (2) the rapid urease test, or (3) the ^{13}C-urea breath test. Tumors were categorized according to their location (i.e., upper [U], middle [M], or lower third [L]) and circumference (i.e., anterior wall [A], posterior wall [P], greater curvature [G], or lower curvature [L]) in the stomach. Atrophic gastritis patterns were evaluated using the Kimura and Takemoto classification[19].

Study outcomes

The outcomes of the study were as follows: intragastric pH levels prior to ESD, the frequency of intraoperative major bleeding, procedure time, *en bloc* resection rate, curability, ulcer reduction rate 14 days after ESD, and adverse events. Specifically, gastric juice was collected using an irrigation tube (PW-6P-1; Olympus Optical, Tokyo, Japan).

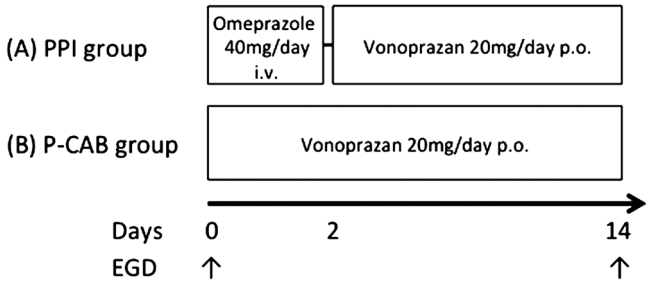

Figure 1 Study protocol.

pH was determined using a test paper (range pH 3.4–6.4; Advantec Toyo, Tokyo, Japan). Major intraoperative bleeding was defined as extensive bleeding requiring the use of hemostatic forceps (Coagrasper; FD-411QR; Olympus) to achieve complete hemostasis[20]. Procedure times were recorded as the time frame between marking and completion of tumor removal. Ulcer reduction rate was determined using the following formula: (1 − ulcer area on post-ESD day 14 / ulcer area on post-ESD day 0) ×100 (%). Of note, the ulcer area was calculated by the following formula: (major axis × minor axis) (mm^2). They were determined by means of a bendable endoscopic measuring device (M2-3; Olympus). Adverse events included perforation during the procedure and postoperative bleeding. We defined perforation as when we could visualize endoscopically either an extramural organ or fat outside the stomach's muscle layer and observe free air by abdominal radiography or computed tomography during or within four weeks post-ESD. Postoperative bleeding was defined as either a decrease in blood hemoglobin levels >2 g/dL or clinical evidence of bleeding due to the ESD procedure, combined with the occurrence of hematemesis and melena, the presence of bleeding on endoscopy, or a combination of unstable vital signs from completion to 4 weeks after the procedure.

ESD

ESD techniques have been extensively described in detail elsewhere[4]. The procedure was performed with a FlushKnife-BTS (DK2625S; FUJIFILM Medical, Tokyo, Japan). A single endoscopist who performed over 600 cases of ESD executed the technique. To prevent intraoperative bleeding, the operator carefully identified blood vessels in the surgical field and thermally coagulated and subsequently cut the blood vessels (preventative coagulation). Preventative coagulation was indicated for vessels with a diameter of >1 mm, as compared to the tip of the FlushKnife with a 0.9-mm diameter[20]. When vessels did not turn whitish after coagulation, hemostatic forceps were used. Thereafter, lesions were dissected at a deep layer of the submucosa. Following the ESD procedure, we first carefully identified the artificial ulcer base and then coagulated the exposed vessels with

hemostatic forceps. Vessels were also coagulated in the absence of bleeding[21]. Measurement and histological classification were performed on the resected specimens according to the criteria of the Japanese Gastric Cancer Association[22]. Lesions were then evaluated for curability.

Follow-up

We did not perform a second-look endoscopy. In absence of any complications, patients resumed food intake on post-ESD day 2. All patients were discharged within seven days following ESD. A follow-up endoscopy was performed 14 days after ESD.

PSM

The baseline characteristics of patients receiving ESD therapy included multiple stratification factors. Therefore, PSM was used to minimize potentially confounding factors and selection biases and to identify controls within the study-patient group. We used 10 possible confounders as matching factors. Nine variables based on previous reports were used: age, sex, comorbidity (chronic kidney disease), lesion location, lesion circumference, macroscopic type, specimen size, tumor depth, and histology[20, 23–26]. Atrophic gastritis patterns were significantly different in univariate analysis. In a multivariate logistic regression analysis, the confounders were included as independent variables, while therapy with P-CAB alone was included as the dependent variable. The propensity score for therapy with P-CAB alone was calculated through logistic regression analysis. Following the estimation of the propensity score, control patients and those of the P-CAB group were matched. Optimal matching was achieved at a 1:1 ratio, and we used a caliper coefficient of 0.1 for the logit of the propensity score without replacement. Covariate balance was measured using the standardized difference, whereby an absolute standardized difference above 10% represents meaningful imbalance.

Statistical analysis

Statistical analysis of the clinical and endoscopic data was done with the χ^2 test for categorical data and Student's t-test for numerical data for univariate analysis. We determined both absolute differences and *P*-values. We considered $P<0.05$ as statistically significant. All statistical analyses were performed with JMP version 12.0 (SAS Institute, Cary, NC, USA).

Ethics

The study was performed in accordance with the principles of the Declaration of Helsinki. The ethics committee of the Hiraka General Hospital approved the study. Written informed consent from all patients and their families was obtained to perform endoscopic submucosal dissection and publish the data.

Results

Baseline characteristics

Table 1 shows the baseline characteristics for both the PPI group and the P-CAB group. We observed a significant difference in the two groups for the following characteristics: atrophic gastritis pattern ($P=0.003$), chronic kidney disease ($P=0.017$), lesion location ($P=0.017$), and specimen size ($P=0.023$). Of note, other patient characteristics and lesion characteristics were not significantly different between groups. Table 2 describes the matched variables and outcomes in both groups after PSM. Forty-three pairs of patients were matched and compared with regard to outcomes. The propensity score model was well-calibrated (AUC=0.77) and optimally matched (Caliper: 0.1, standardized difference < 0.1) in terms of baseline patients and lesion characteristics in both groups.

Treatment outcomes in the P-CAB and PPI groups after PSM

Table 3 describes outcomes in both groups. All cases had indicated intragastric pH levels of 6.4 pre-ESD. The ulcer size reduction at 14 days post-ESD was similar between groups (mean [SD]; 75.32% [11.30] in the PPI group vs. 78.76% [13.18] in the P-CAB group, $P=0.196$). Postoperative bleeding occurred in 1 (2.3%) patient in the PPI group and in 0 (0.0%) patients in the P-CAB group ($P=0.315$). Other outcomes (frequency of intraoperative major bleeding, procedure time, *en bloc* resection rate, curability, and perforation) were the same in both groups, specifically with a low incidence of adverse events. No treatment-related deaths were observed.

Discussion

The aim of the present study was to assess the effectiveness of PPI injection compared to P-CAB administration alone during the perioperative period of gastric ESD using PSM. We demonstrate that there is no significant difference between PPI injection and vonoprazan tablets alone in terms of treatment outcomes and adverse events.

Acid-suppressing agents have been used mainly to prevent postoperative bleeding post-ESD.In an earlier study, Berstad reported that digestion of fibrin clots by gastric juice indicated no activity at pH >4[27]. Gastric acid inhibition to maintain a neutral pH could stabilize blood clots and prevent recurrent bleeding[28, 29]. Previous studies have reported that PPIs were more effective than histamine-2-receptor antagonists (H_2RAs) in controlling bleeding in patients undergoing ESD[30]. Therefore, the administration of PPIs has become a standard therapy to manage iatrogenic gastric ulcers post-ESD. On the contrary, bleeding events mostly occurred within 24 hours and extended up to 2 weeks post-ESD[14].

Table 1 Baseline characteristics of the 150 superficial gastric neoplasms that underwent ESD

	PPI Group (n=80)	P-CAB group (n=70)	*P*	ASD
Patient characteristics				
Age, median [range] (y)	73 [47–88]	73 [54–89]	0.068*	0.300
Sex				
Male/Female	63/17	52/18	0.519†	0.105
H.pylori status				
positive/negative/post eradication	63/4/13	54/2/14	0.693†	0.110
Atrophic gastritis pattern				
open/closed/none	58/19/3	65/3/2	0.003†	0.583
Comorbities (positive/negative)				
Diabetes mellitus	3/77	1/69	0.379†	0.146
Chronic kidney disease (eGFR <30)	1/79	7/63	0.017†	0.386
Liver cirrhosis	0/80	1/69	0.283†	0.170
Lesion characteristics				
Lesion location				
U/M/L	13/33/34	24/17/29	0.017†	0.046
Lesion circumference				
A/P/G/L	13/22/20/25	7/21/17/25	0.190†	0.185
Macroscopic type				
Flat/Depressed	37/43	25/45	0.191†	0.215
Specimen size				
mean [SD] (mm^2)	1,706.2 [124.41]	1,317.4 [938.3]	0.023*	0.580
Tumor depth				
M/SM	73/7	62/8	0.585†	0.160
Histology				
differentiated/pooly differentiated	73/7	62/8	0.973†	0.069

H.pylori: Helicobacter pylori; U: upper third; M: middle third; L: lower third of the stomach; A: anterior wall; P: posterior wall; G: greater curvature; L: lower curvature; SD: standerd deviation; ASD: Absolute standerdized difference. *: student's t-test; †: χ^2 test.

Therefore, the rapid inhibition of gastric acid secretion is necessary via acid-suppressing agents. However, previous studies have revealed a delay in the sustained reduction of acid secretion with PPIs. Maximum efficacy was typically reached only after 3–5 days of standard dosing[31]. Clinically, such controversial data has created concerns over gastric ESD. Uedo *et al.* reported that administration of rabeprazole 1 day before ESD might be sufficient in increasing intragastric pH at the time of ESD[32]. In contrast, One *et al.* showed no additional benefit in the 1-day preoperative administration of omeprazole and a prior increase of intragastric pH in preventing bleeding post-ESD[33].

For patients with upper gastrointestinal bleeding, intravenous injection of omeprazole was developed in 2001, while the injection of lansoprazole was developed in 2006. A single infusion of PPIs is known to quickly raise intragastric pH to above 4[34]. As a consequence, it has historically been used for gastric ESD, similar to hemorrhagic peptic ulcer treatment. However, there is little evidence available to date in its use in the perioperative period of ESD. Ishido *et al.* reported a similar effectiveness in the 1-day preoperative administration of lansoprazole tablets compared to intravenous lansoprazole in a randomized controlled trial (RCT)[5] for bleeding prevention post-ESD.

The novel therapeutic agent vonoprazan rapidly suppresses gastric acid secretion[6]. The drug is reported to achieve steady-state acid levels on the first day. Additionally, it raises intragastric pH above 4 by 4 hours after the first dose[6, 35]. In the present study, the first administration of omeprazole injection or vonoprazan was performed 8 hours prior to the ESD procedure. All the cases in both the PPI and the P-CAB group had a pH >6.4 at the beginning of ESD.

The following are the medication costs for 14 days of treatment in the present study. Specifically, total costs were estimated by the Japan Ministry of Health, Labour and Welfare in 2018 to be 4,039.2 yen for the PPI group (2 days of omeprazole injection and 12 days of vonoprazan tablets) and 2,822.4 yen for the P-CAB group (14 days of vonoprazan tablets). Importantly, treatment with P-CAB alone is only 70% of the cost of the standard PPI treatment. In addition, intravenous infusion of omeprazole (b.i.d.) would not be necessary in the P-CAB group for the first two days. Therefore, we believe that because of low costs, decreased effort, and safety, P-CAB administration alone is advantageous

Table 2 Matching variables after propensity score analysis

	PPI Group (n=43)	P-CAB group (n=43)	*P*	ASD
Patient characteristics				
Age, median [range] (y)	74 [47–88]	73 [54–87]	0.663*	0.094
Sex				
Male/Female	31/12	30/13	0.519†	0.051
Atrophic gastritis pattern				
open/closed/none	39/2/2	38/3/2	0.899†	0.099
Comorbities (positive/negative)				
Chronic kidney disease (eGFR <30)	1/42	1/42	1.000†	0.000
Lesion characteristics				
Lesion location				
U/M/L	12/12/19	12/11/20	0.966†	0.021
Lesion circumference				
A/P/G/L	6/12/10/15	4/14/11/14	0.888†	0.095
Macroscopic type				
Flat/Depressed	19/24	17/26	0.662†	0.094
Specimen size				
mean [SD] (mm^2)	1,458.1 [1,041.4]	1,389.5 [1,067.35]	0.764*	0.065
Tumor depth				
M/SM	38/5	40/3	0.456†	0.089
Histology				
differentiated/pooly differentiated	37/6	38/5	0.747†	0.005

H.pylori: Helicobacter pylori; U: upper third; M: middle third; L: lower third of the stomach; A: anterior wall; P: posterior wall; G: greater curvature; L: lower curvature; SD: standerd deviation; ASD: Absolute standerdized difference. *: student's t-test; †: χ^2 test.

Table 3 Treatment outcomes after propensity score matching

	PPI Group (n=43)	P-CAB group (n=43)	*P*
Intra-gastric pH level 6.4 (%)	43/43 (100.0)	43/43 (100.0)	1.000†
Frequency of major bleeding			
median [range] (times)	0 [0–4]	0 [0–5]	0.527*
Procedure time			
mean [SD] (min.)	72.37 [51.78]	72.93 [41.37]	0.956*
En bloc resection rate (%)	43/43 (100.0)	43/43 (100.0)	1.000†
Curability (eCura)			
A/B/C1/C2	32/10/0/1	35/7/0/1	0.717†
Ulcer reduction rate 14 days after ESD			
mean [SD] (%)	75.32 [11.30]	78.76 [13.18]	0.196*
Adverse events (positive/negative)			
Perforation (%)	0/43 (0.0)	0/43 (0.0)	1.000†
Postoperative bleeding (%)	1/43 (2.3)	0/43 (0.0)	0.315†

SD: standerd deviation; *: student's t-test; †: χ^2 test.

compared with PPI injection.

The present study has several limitations as follows. Firstly, it was done in a single institution and only a relatively small number of patients were retrospectively enrolled. Secondly, only an experienced endoscopist performed all the ESD procedures. However, we believe that a consistent level of technical expertise and identical therapeutic strategies between operators could positively influence the assessment of treatment outcomes and adverse events. Finally, we did not enroll patients on antithrombotic therapy in this study. In the future, a multicenter large-scale prospective RCT with or without antithrombotic therapy will be warranted to determine the influence of oral administration of P-CAB alone on the effects and outcomes of ESD.

Conclusion

Oral administration of P-CAB alone was as effective as PPI injection. We observed a low incidence of adverse events. Therefore, we believe that PPI injection might be safely omitted from the procedure of gastric ESD considering its cost and high labor.

Conflicts of interest: All authors (Saki Fushimi, Yohei Horikawa, Hiroya Mizutamari, Nobuya Mimori, Yuhei Kato, and Sayaka Sato) declare that they have no conflicts of interest or financial ties to disclose.

References

1. Ono H, Kondo H, Gotoda T, *et al*. Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001; 48: 225–229. [Medline] [CrossRef]
2. Yahagi N, Uraoka T, Ida Y, *et al*. Endoscopic submucosal dissection using the flex and the dual knife. Tech Gastrointest Endosc 2011; 13: 74–78. [CrossRef]
3. Oyama T, Tomori A, Hotta K, *et al*. Endoscopic submucosal dissection of early esophageal cancer. Clin Gastroenterol Hepatol 2005; 3(Suppl 1): S67–S70. [Medline] [CrossRef]
4. Toyonaga T, Nishino E, Man-I M, *et al*. Principles of quality controlled endoscopic submucosal dissection with appropriate dissection level and high quality resected specimen. Clin Endosc 2012; 45: 362–374. [Medline] [CrossRef]
5. Ishido K, Tanabe S, Azuma M, *et al*. Comparison of oral and intravenous lansoprazole for the prevention of bleeding from artificial ulcers after endoscopic submucosal dissection for gastric tumors: a prospective randomized phase II study (KDOG 0802). Surg Endosc 2018; 32: 2939–2947. [Medline] [CrossRef]
6. Jenkins H, Sakurai Y, Nishimura A, *et al*. Randomised clinical trial: safety, tolerability, pharmacokinetics and pharmacodynamics of repeated doses of TAK-438 (vonoprazan), a novel potassium-competitive acid blocker, in healthy male subjects. Aliment Pharmacol Ther 2015; 41: 636–648. [Medline] [CrossRef]
7. Kagawa T, Iwamuro M, Ishikawa S, *et al*. Vonoprazan prevents bleeding from endoscopic submucosal dissection-induced gastric ulcers. Aliment Pharmacol Ther 2016; 44: 583–591. [Medline] [CrossRef]
8. Maruoka D, Arai M, Kasamatsu S, *et al*. Vonoprazan is superior to proton pump inhibitors in healing artificial ulcers of the stomach post-endoscopic submucosal dissection: a propensity score-matching analysis. Dig Endosc 2017; 29: 57–64. [Medline] [CrossRef]
9. Takahashi K, Sato Y, Kohisa J, *et al*. Vonoprazan 20 mg *vs* lansoprazole 30 mg for endoscopic submucosal dissection-induced gastric ulcers. World J Gastrointest Endosc 2016; 8: 716–722. [Medline] [CrossRef]
10. Tsuchiya I, Kato Y, Tanida E, *et al*. Effect of vonoprazan on the treatment of artificial gastric ulcers after endoscopic submucosal dissection: prospective randomized controlled trial. Dig Endosc 2017; 29: 576–583. [Medline] [CrossRef]
11. Horikawa Y, Mizutamari H, Mimori N, *et al*. Short-term efficacy of potassium-competitive acid blocker following gastric endoscopic submucosal dissection: a propensity score analysis. Scand J Gastroenterol 2018; 53: 243–251. [Medline] [CrossRef]
12. Kakushima N, Fujishiro M, Kodashima S, *et al*. Histopathologic characteristics of gastric ulcers created by endoscopic submucosal dissection. Endoscopy 2006; 38: 412–415. [Medline] [CrossRef]
13. Lee SH, Lee CK, Chung IK, *et al*. Optimal duration of proton pump inhibitor in the treatment of endoscopic submucosal dissection-induced ulcers: a retrospective analysis and prospective validation study. Dig Dis Sci 2012; 57: 429–434. [Medline] [CrossRef]
14. Oda I, Gotoda T, Hamanaka H, *et al*. Endoscopic submucosal dissection of early gastric cancer: technical feasibility, operation time, and complications from a large consecutive series. Dig Endosc 2005; 17: 54–58. [CrossRef]
15. Park YM, Cho E, Kang HY, *et al*. The effectiveness and safety of endoscopic submucosal dissection compared with endoscopic mucosal resection for early gastric cancer: a systematic review and metaanalysis. Surg Endosc 2011; 25: 2666–2677. [Medline] [CrossRef]
16. Ross ME, Kreider AR, Huang YS, *et al*. Propensity score methods for analyzing observational data like randomized experiments: challenges and solutions for rare outcomes and exposures. Am J Epidemiol 2015; 181: 989–995. [Medline] [CrossRef]
17. Gotoda T, Yanagisawa A, Sasako M, *et al*. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer 2000; 3: 219–225. [Medline] [CrossRef]
18. Japanese Gastric Cancer Association Gastric Cancer Treatment Guideline of 5th edition. 2018.
19. Kimura K, Takemoto T. An endoscopic recognition of the atrophic border and its significance in chronic gastritis. Endoscopy 1969; 1: 87–97. [CrossRef]
20. Horikawa Y, Toyonaga T, Mizutamari H, *et al*. Feasibility of knife-coagulated cut in gastric endoscopic submucosal dissection: a case-control study. Digestion 2016; 94: 192–198. [Medline] [CrossRef]
21. Takizawa K, Oda I, Gotoda T, *et al*. Routine coagulation of visible vessels may prevent delayed bleeding after endoscopic submucosal dissection—an analysis of risk factors. Endoscopy 2008; 40: 179–183. [Medline] [CrossRef]
22. Japanese Gastric Cancer Association Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer 2011; 14: 101–112. [Medline] [CrossRef]
23. Toyonaga T, Nishino E, Hirooka T, *et al*. Intraoperative bleeding in endoscopic submucosal dissection in the stomach and strategy for prevention and treatment. Dig Endosc 2006; 18: S123–S127. [CrossRef]
24. Jeon SW, Jung MK, Cho CM, *et al*. Predictors of immediate bleeding during endoscopic submucosal dissection in gastric lesions. Surg Endosc 2009; 23: 1974–1979. [Medline] [CrossRef]
25. Gotoda T, Yamamoto H, Soetikno RM. Endoscopic submucosal dissection of early gastric cancer. J Gastroenterol 2006; 41: 929–942. [Medline] [CrossRef]
26. Kikuchi D, Iizuka T, Hoteya S, *et al*. Usefulness of endoscopic ultrasound for the prediction of intraoperative bleeding of endoscopic submucosal dissection for gastric neoplasms. J Gastroenterol Hepatol 2011; 26: 68–72. [Medline] [CrossRef]
27. Berstad A. Management of acute upper gastrointestinal bleeding. Scand J Gastroenterol Suppl 1982; 75: 103–108. [Medline]

28. Oh JH, Choi MG, Dong MS, *et al*. Low-dose intravenous pantoprazole for optimal inhibition of gastric acid in Korean patients. J Gastroenterol Hepatol 2007; 22: 1429–1434. [Medline] [CrossRef]
29. Lee SY, Kim JJ, Lee JH, *et al*. Healing rate of EMR-induced ulcer in relation to the duration of treatment with omeprazole. Gastrointest Endosc 2004; 60: 213–217. [Medline] [CrossRef]
30. 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: 315–320. [Medline] [CrossRef]
31. Shimatani T, Inoue M, Kuroiwa T, *et al*. Acid-suppressive effects of rabeprazole, omeprazole, and lansoprazole at reduced and standard doses: a crossover comparative study in homozygous extensive metabolizers of cytochrome P450 2C19. Clin Pharmacol Ther 2006; 79: 144–152. [Medline] [CrossRef]
32. 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: 1610–1616. [Medline] [CrossRef]
33. Ono S, Kato M, Ono Y, *et al*. Effects of preoperative administration of omeprazole on bleeding after endoscopic submucosal dissection: a prospective randomized controlled trial. Endoscopy 2009; 41: 299–303. [Medline] [CrossRef]
34. Andersen J, Ström M, Naesdal J, *et al*. Intravenous omeprazole: effect of a loading dose on 24-h intragastric pH. Aliment Pharmacol Ther 1990; 4: 65–72. [Medline] [CrossRef]
35. Sakurai Y, Mori Y, Okamoto H, *et al*. Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects—a randomised open-label cross-over study. Aliment Pharmacol Ther 2015; 42: 719–730. [Medline] [CrossRef]