Gastrointestinal Tract

ORIGINAL ARTICLE

Comparative efficacy of esomeprazole *vs.* rabeprazole in post-endoscopic submucosal dissection gastric ulcers: a prospective randomized trial

Kazuya Akahoshi[1,*], Shigeki Osada[2], Kazuki Inamura[2], Yuki Shiratsuchi[2], Kazuaki Akahoshi[2], Masafumi Oya[3], Hidenobu Koga[4]

[1]Preventive Medicine Center, Aso Iizuka Hospital, Iizuka 820-8505, Japan
[2]Department of Gastroenterology, Aso Iizuka Hospital, Iizuka 820-8505, Japan
[3]Department of Pathology, Aso Iizuka Hospital, Iizuka 820-8505, Japan
[4]Clinical Research Support Office, Aso Iizuka Hospital, Iizuka 820-8505, Japan

ABSTRACT

Background and objectives: There is inadequate data on the clinical outcomes of proton pump inhibitors in patients with post-endoscopic submucosal dissection (ESD) gastric ulcers (PESDGU). The clinical course of PESDGU is affected by various ESD methods, including the types of devices and endoscopists' skills. No previous reports have compared the clinical outcomes of different proton pump inhibitors for PESDGU healing in patients who underwent the same ESD method using the same device by the same well-trained endoscopist. This study aims to compare the clinical outcome of esomeprazole *vs*. rabeprazole in PESDGU using the same ESD method and by the same endoscopist. **Methods:** Sixty patients with gastric tumors participated in this randomized clinical trial. Patients who underwent ESD using the Clutch Cutter (ESDCC) method by the same endoscopist were prospectively randomly assigned to esomeprazole 20 mg (EM) or rabeprazole 20 mg (RM) monotherapy groups. All patients received 20 mg omeprazole intravenously daily for the first 2 days post-ESDCC, followed by oral administration of EM or RM for 8 weeks. All patients remained hospitalized for 7 days post-operation to monitor any ESD-related complications. Esophagogastroduodenoscopy was performed 8 weeks post-ESD to evaluate the healing status of each artificial ulcer. **Results:** Of the 60 patients in this study, 30 each were assigned to the EM and RM groups. Eight patients from both groups did not complete the regimen and were excluded. Exactly 52 patients completed the study, with 27 and 25 in the EM and RM groups, respectively. There were no significant differences in the demographic characteristics of the two groups. There were no post-ESD perforations in either group. Post-ESD bleeding occurred in one patient in the RM group 5 days post-ESD. Scarring rates at the endpoint 8 weeks after ESD in the EM and RM groups were 96% and 76%, respectively. There were no significant differences between the two groups in the scarring stage (S1 or S2) at 8 weeks post-ESD. **Conclusion:** EM and RM have equivalent therapeutic effects on PESDGUs.

Key words: endoscopic submucosal dissection, Clutch Cutter, artificial ulcer, gastric tumors, proton pump inhibitors

INTRODUCTION

With improvements in endoscopic therapy for patients with early gastric cancer (EGC), endoscopic submucosal dissection (ESD) has become a widespread alternative to surgery.[1,2] ESD enables en-bloc resection of gastric

***Corresponding Author:**
Kazuya Akahoshi, Preventive Medicine Center, Aso Iizuka Hospital, 3-83 Yoshio, Iizuka 820-8505, Japan. E-mail: kakahoshi2@aol.com. https://orcid.org/0000-0002-1095-6546

Received: 29 May 2023; Revised: 26 July 2023; Accepted: 16 August 2023; Published: 21 August 2023
https://doi.org/10.54844/git.2023.406

lesions, regardless of size or location. Therefore, very large artificial ulcers result from ESD.[3,4] Recently, two major proton pump inhibitors (PPI) in Japan, esomeprazole[5,6] and rabeprazole[7,8] have been used to facilitate the healing of artificial ulcers after gastric ESD. However, it is still unknown whether the difference in the type of PPI is related to the cure rate of artificial ulcers after ESD and the occurrence rate of complications. Furthermore, the clinical course of post-endoscopic submucosal dissection gastric ulcer (PESDGU) is affected by the ESD method, including the types of devices[9–11] and the endoscopist's skills.[12,13] There are no previous reports on the efficacy of PPIs for PESDGU healing in patients who underwent the same single-device ESD method by the same endoscopist. Therefore, we performed a prospective randomized controlled study comparing the effects of esomeprazole and rabeprazole on PESDGU healing in patients who underwent the same single-device ESD method using the Clutch Cutter (ESDCC)[14] by the same endoscopist.

MATERIALS AND METHODS

Ethics

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Aso Iizuka Hospital (No12079). This study was assigned to "UMIN ID:000024002".

Patients

Between January 2013 and December 2014, 60 consecutive patients with early gastric cancer or gastric adenoma considered curable with ESD at Aso Iizuka Hospital were enrolled in the study. The clinical indications for ESDCC were as follows: (1) adenomas; (2) differentiated-type intramucosal cancers without ulcer findings; (3) differentiated-type intramucosal cancers less than 3 cm in size with ulcer findings; or (4) undifferentiated-type mucosal cancer less than 2 cm in size without ulceration. None of the patients had a history of upper gastrointestinal surgery. All patients agreed to participate in the study and were treated with ESDCC.

ESD method using the Clutch Cutter

The detailed technical procedures for ESDCC have been reported previously.[14] ESDCC in all cases was performed by a single well-trained endoscopist (KA). ESDCC was mainly performed using a single-channel therapeutic endoscope (EG-450RD5 or EG-530RD5; Fujifilm, Tokyo, Japan). A long transparent hood (F-01; Top Co. Ltd., Tokyo, Japan) was attached to the tip of the endoscope to facilitate submucosal dissection by elevating the lesion. A high-frequency electrosurgical unit (VIO 300D; Erbe, Tübingen, Germany) was used. Circumferential markings were made using a Clutch Cutter (CC) in closed mode. Hyaluronic acid solution (MucoUp; Johnson and Johnson, Tokyo, Japan) with diluted epinephrine (0.0002%) and indigo carmine (0.0002%) was injected into the submucosal layer to lift the lesion. The target mucosal and submucosal tissue layers were then grasped, lifted up, and cut using a CC. Finally, the lesion was completely resected using CC. Coagulation with CC was used to arrest any bleeding that occurred during the procedure. The endo-cut Q mode (effect 2, duration 3, interval 1) was used for cutting, and the soft coagulation mode at 100 W (effect 5) was used for hemostatic treatment.

Study design

In this prospective randomized clinical trial, patients were assigned randomly (computer-assisted randomization) and evenly to either the esomeprazole monotherapy (EM) group or the rabeprazole monotherapy (RM) group. After ESDCC, all patients received intravenous administration of 20 mg omeprazole (Omepral® injection; Astra Zeneca Co., Osaka, Japan) daily for the first 2 days, followed by 8 weeks of oral administration of EM or RM. The EM group was administered 20 mg oral esomeprazole (Nexium®; Astra-Zeneca Co., Ltd. Osaka, Japan), whereas the RM group was treated daily with 20 mg of oral rabeprazole (Pariet®; Eisai Co., Ltd. Tokyo, Japan). All patients stayed in the hospital 7 days after the procedure to monitor for any complications. Esophagogastroduodenoscopy was performed 8 weeks post-ESD to evaluate the healing status of each artificial ulcer.

Endpoints

The primary endpoint of this study was the rate of post-ESDCC bleeding and perforation. The secondary endpoint evaluated in the study was the proportion of patients whose ulcer had progressed to the scarring-stage, defining complete healing of the artificial ulcer at 8 weeks post-ESDCC.

Assessment of severe complications

Regarding complications, "bleeding" was defined as either a massive hemorrhage requiring blood transfusion during the procedure or a postoperative hemorrhage requiring urgent endoscopic hemostatic treatment. Perforation was assessed by physical examination, endoscopic observation, and free air on plain radiography or computed tomography. All patients stayed in the hospital for 7 days following the procedure. Serial hematocrits were obtained 1, 2, and 7 days after therapy, and patients were assessed daily for hematemesis and hematochezia.

Assessment of ulcer healing

The six-stage Sakita and Miwa scale of gastric ulcers [active (A1, A2), healing (H1, H2), and scarring (S1, S2)][15] was used to classify the degree of ulcer healing in patients from the two PPIs (Table 1). The S-stage was defined as the healing of the artificial ulcer.

Statistical analyses

The data were analyzed using Fisher's exact test, *t*-test, Wilcoxon rank-sum test, Welch's test, and χ^2-test. Clinical significance was set at $P < 0.05$. All statistical analyses were conducted with a statistical software package (SAS version 9.2 and JMP version 8.0.1, SAS Institute Inc, NC, USA).

RESULTS

Patients flow

Of the 60 patients with EGC who provided written informed consent and were enrolled in this study, 30 patients each were assigned to the EM and RM groups. Three patients in the EM group (two underwent surgery for submucosal invasion, and one did not undergo examination) and five patients in the RM group (two underwent surgery for submucosal invasions, one underwent surgery for discontinuation of ESDCC due to technical difficulty in resection of early gastric cancer spreading across the pyloric ring, and two did not receive examination) did not complete the regimen and were excluded. The remaining 52 patients completed the study with 27 patients and 25 patients, respectively in the EM and RM groups.

Baseline demographic data

There were no significant differences in the demographic characteristics between the two groups, as summarized in Table 2.

Primary endpoint (rate of post-ESDCC bleeding and perforation)

Table 3 shows the incidence of post-ESDCC bleeding and perforation in the two groups. No serious adverse events occurred in either of the groups. In the RM group, one patient experienced bleeding from a post-ESDCC artificial ulcer. Tarry stools were observed on the 5th day after ESDCC, and the patient underwent endoscopy. Bleeding was stopped by endoscopic coagulation of the exposed blood vessel within the ulcer using hemostatic forceps. PPI treatment was continued. The patient was discharged on the 10th day after ESDCC. There were no post-ESDCC perforations in either group. There were no significant differences in the rates of post-ESDCC bleeding and perforation between the two groups.

Secondary endpoint (rate of progression to scarring-stage)

Table 4 compares the distribution of ulcer stages (Figure 1) in both groups. Scarring rates at the endpoint 8 weeks after ESDCC in the EM and RM groups were 96% (26/27) and 76% (19/25), respectively. There were no significant differences in the rate of progression to scarring-stage (S1 or S2) at 8 weeks after ESDCC between the two groups.

DISCUSSION

ESD has eliminated the size limitation of early gastric tumors, the objective of endoscopic treatment, and has expanded its indication.[16,17] As a result, ESD produces a large PESDGU, and the risk of bleeding and perforation from PESDGU is higher than from gastric ulcers induced by conventional EMR.[18] It also became clear that it took time for the ulcers to heal. It is well known that the rate of gastric ulcer healing and bleeding is influenced by pH levels.[19] Therefore, strong acid secretion inhibitors, including histamine2-receptor antagonists (H2RAs), proton pump inhibitors (PPI), and potassium-competitive acid blockers (P-CABs), are usually used to treat PESDGU. Currently, PPIs are the most common and relatively potent acid secretion inhibitors worldwide.[20] It is unclear which PPI is the best medicine that can reduce the risk of post-ESD bleeding and perforation and shorten the time of ulcer healing. Esomeprazole, an S-isomer of omeprazole, is a new form of PPI reported to show stronger inhibition of gastric acid secretion than conventional PPIs.[21] In this study, we compared the efficacy of esomeprazole and rabeprazole in ulcer healing following ESD. Furthermore, the clinical course, including adverse events of PESDGU, is affected by the ESD method, including the type of device and the endoscopist's skill.[11–13] Therefore, in this study, ESD was performed by the same well-trained endoscopist (first author KA) using the same device (CC) to eliminate differences in ESD devices and endoscopists' skills.

Post-ESD bleeding is the most common complication of ESD. Endoscopic treatment can control most post-ESD bleeding; however, it sometimes leads to life-threatening conditions requiring blood transfusion or emergency angiography.[3,4,22] The incidence of post-ESD bleeding using EM and RM has been reported to be 0–2%[5,6] and 1.8%–2.7%,[7,8] respectively. In this study, only one patient (4%) in the RM group experienced bleeding from the post-ESDCC artificial ulcer on the 5th day after ESDCC. No post-ESDCC bleeding episodes occurred in the EM group. There were no significant differences in the rate of post-ESDCC bleeding between the two groups.

Table 1: Sakita and Miwa's gastric ulcer staging[15]

Ulcer stage	Typical findings
A1 (active stage 1)	Ulcer that contains mucus coating, with marginal elevation because of edema
A2 (active stage 2)	Mucus-coated ulcers with discrete margins and less edema than active stage 1
H1 (healing stage 1)	Unhealed ulcer covered by regenerating epithelium < 50%, with or without converging folds
H2 (healing stage 2)	Ulcer with a mucosal break but almost covered with regenerating epithelium
S1 (scar stage 1)	Red scar with rough epithelialization without mucosal break
S2 (scar stage 2)	White scar with complete re-epithelialization

Table 2: Baseline demographic data of esomeprazole and rabeprazole groups

	Esomeprazole	Rabeprazole	*P* value*
Gender (Male:Female)	16:11	13:12	0.7804
Age (mean ± SD)	71.3 ± 8.0	72.1 ± 8.1	0.7381
H. pylori infection (positive:negative)	12:15	15:10	0.2834
Anticoagulant (existence:non-existence)	2:25	2:23	1.0000
Histologic diagnosis of resected specimen (adenocarcinoma:adenoma)	23:4	17:8	0.1933
Location (upper:middle:lower)	9:9:9	5:11:9	0.5346
Mean diameter of the lesions (mean ± SD mm)	16.9 ± 9.7	17.7 ± 14.8	0.6271
Mean diameter of the resected specimens (mean ± SD mm)	44.7 ± 11.8	42.6 ± 19.4	0.6545

*Statistical significance was analyzed using Fisher's exact test, *t*-test, Wilcoxon rank sum test, and Welch's test.

Table 3: Post-ESDCC bleeding and perforation following EM or RM therapy

	Esomeprazole	Rabeprazole	*P* value*
Total number of patients	27	25	
Post-ESD bleeding, *n* (%)			
Positive	0 (0)	1 (4)	
Negative	27 (100)	24 (96)	0.4807
Post-ESD perforation, *n* (%)			
Positive	0 (0)	0 (0)	
Negative	27 (100)	25 (100)	0.9710

*Statistical significance was analyzed using Fisher's exact test and χ-test. ESDCC: endoscopic submucosal dissection using Clutch cutter; ESD: endoscopic submucosal dissection.

Table 4: Distribution of ulcer stages 8 weeks post-ESDCC following esomeprazole/rabeprazole therapy

	Esomeprazole	Rabeprazole	*P* value*
Total number of patients, *n* (%)	27	25	
A1	0 (0)	0 (0)	
A2	0 (0)	0 (0)	
H1	0 (0)	1 (4)	
H2	1 (3.7)	5 (20)	0.9710
S1	25 (92.6)	19 (76)	
S2	1 (3.7)	0 (0)	

*Statistical significance was analyzed by Fisher's exact test. ESDCC: Endoscopic submucosal dissection using Clutch cutter.

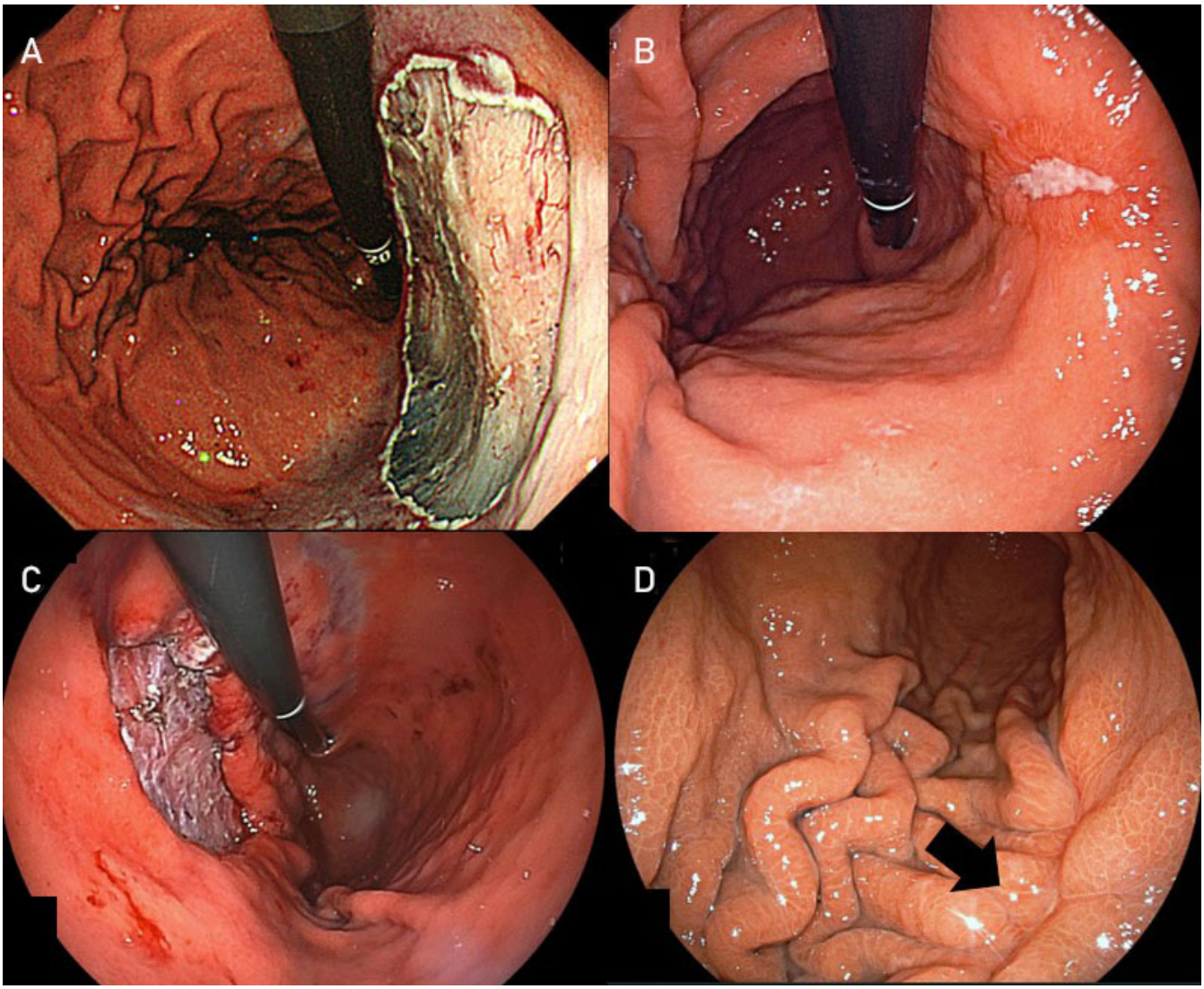

Figure 1. Endoscopic images of healing process of artificial ulcers immediately after ESDCC and 8 weeks later. **A**. A1 stage artificial ulcer on lesser curvature of gastric body immediately after ESDCC (esomeprazole group). **B**. H2 stage artificial ulcer on lesser curvature of gastric body on 8 weeks after ESDCC (esomeprazole group). **C**. A1 stage artificial ulcer on greater curvature of gastric body immediately after ESDCC (rabeprazole group). **D**. S2 stage artificial ulcer scar on greater curvature of gastric body on 8 weeks after ESDCC (rabeprazole group).

Post-ESD perforation is a severe adverse event associated with ESD. Delayed perforation occurred in 0.4% of gastric ESD cases, and 35.0% required emergency surgery.[22] One possible cause is muscle layer damage due to excessive intraoperative electrothermal currents. Incidence of post-ESD perforation under EM and RM are both reported as 0%.[5–8] In this study, there were no post-ESDCC perforation episodes in either group of patients.

Theoretically, stronger acid-suppressing agents are expected to heal artificial ulcers faster. The rate of scar change (artificial ulcer healing) at week 8 under EM and RM has been reported to be 84.6%–98%[5,6,23] and 85.5%–88.6%,[8,24] respectively. In this study, the scar change rates at week 8 under EM and RM were 96% and 76%, respectively. There were no significant differences in the rate of scar changes between the two groups.

Although our study was a prospective randomized controlled trial, it had some limitations. First, the sample size was relatively small. Second, this study was conducted at a single center. Further large, multicenter, prospective, randomized controlled trials with more cases are required to validate our findings.

In conclusion, EM and RM have equivalent therapeutic effects in PESDGUs.

DECLARATIONS

Author contributions

Akahoshi K (Kazuya) designed the study; Akahoshi K (Kazuya), Osada S, Inamura K, Shiratsuchi Y, and Oya

M performed the research; Koga H analyzed the data; Akahoshi K (Kazuya) wrote the paper; Akahoshi K (Kazuya) performed ESD; Akahoshi K (Kazuaki) critically revised the article for important intellectual content; all the authors reviewed and approved the final version to be published.

Supported by
Clinical Research Grant from Aso Iizuka Hospital. Research grants from AstraZeneca Co, Ltd.

Acknowledgments
This research was conducted with the assistance of a research grants from AstraZeneca Co, Ltd. We would like to thank Editage (www.editage.com) for English language editing.

Conflict of interest
Kazuya Akahoshi received research grants from AstraZeneca Co. All coauthors declare no potential conflicts of interest.

Data sharing statement
No additional data is available.

REFERENCES

1. Hisada H, Sakaguchi Y, Oshio K, Mizutani S, Nakagawa H, Sato J, *et al.* Endoscopic treatment of superficial gastric cancer: Present status and future. Curr Oncol 2022; 29: 4678-4688.
2. Young E, Philpott H, Singh R. Endoscopic diagnosis and treatment of gastric dysplasia and early cancer: Current evidence and what the future may hold. World J Gastroenterol; 27: 5126-5151.
3. Hatta W, Koike T, Abe H, Ogata Y, Saito M, Jin X, *et al.* Recent approach for preventing complications in upper gastrointestinal endoscopic submucosal dissection. DEN open 2022; 2: e60.
4. Yamamoto Y, Kikuchi D, Nagami Y, Nonaka K, Tsuji Y, Fujimoto Ai, *et al.* Management of adverse events related to endoscopic resection of upper gastrointestinal neoplasms: Review of the literature and recommendations from experts. Dig Endosc 2019; 31; Suppl 1:4-20.
5. Ichida T, Kusano F, Sakai Y. Effects of esomeprazole on the healing process of post-endoscopic submucosal dissection gastric ulcers: A single arm, prospective trial. J Rural Med 2016; 11:41-45.
6. Ishii Y, Yamada H, Sato T, Sue S, Kaneko H, Irie K, *et al.* Effects of vonoprazan compared with esomeprazole on the healing of artificial post-endoscopic submucosal dissection ulcers: A prospective, multicenter, two-arm, randomized controlled trial. Gastroenterol Res Pract 2018.
7. Niimi K, Fujishiro M, Goto O, Kodashima S, Minatsuki C, Hirayama I, *et al.* Prospective single-arm trial of two-week rabeprazole treatment for ulcer healing after gastric endoscopic submucosal dissection. Dig Endosc 2012; 24: 110-116.
8. Nakamura K, Ihara E, Akiho H, Akahoshi K, Harada N, Ochiai T, *et al.* Limited effect of rebamipide in addition to proton pump inhibitor (PPI) in the treatment of post-endoscopic submucosal dissection gastric ulcers: A randomized controlled trial comparing PPI plus rebamipide combination therapy with PPI monotherapy. Gut Liver 2016; 10:917-924.
9. Kakushima N, Fujishiro M. Endoscopic submucosal dissection for gastrointestinal neoplasms. World J Gastroenterol 2008; 14: 2962-2967.
10. Dohi O, Yoshida N, Terasaki K, Azuma Y, Ishida T, Kitae H, *et al.* Efficacy of clutch Cutter for standardizing endoscopic submucosal dissection for early gastric cancer: A propensity score-matched analysis. Digestion 2019; 100: 201-209.
11. Hayashi Y, Esaki M, Suzuki S, Ihara E, Yokoyama A, Sakisaka S, *et al.* Clutch Cutter knife efficacy in endoscopic submucosal dissection for early gastric neoplasms. World J Gastrointest Oncol 2018; 10: 487-495.
12. Yamamoto S, Uedo N, Ishihara R, Kajimoto N, Ogiyama H, Fukushima Y, *et al.* Endoscopic submucosal dissection for early gastric cancer performed by supervised residents: Assessment of feasibility and learning curve. Endoscopy 2009; 41: 923-928.
13. Zhang X, Ly EK, Nithyanand S, Moddayil R, Khodorskiy DO, Neppala S, *et al.* Learning curve for endoscopic submucosal dissection with an untutored, prevalence-based approach in the United States. Clin Gastroenterol Hepatol 2020; 18: 580-588.
14. Akahoshi K, Komori K, Akahoshi K, Tamura S, Osada S, Shiratsuchi Y, *et al.* Advances in endoscopic therapy using grasping-type scissors forceps (with video). World J Gastrointest Surg 2021; 13: 772-787.
15. Sakita T, Fukutomi H. Endoscopic diagnosis. In: Yoshitoshi Y, editor. Ulcer of the stomach and duodenum. Tokyo: Nankodo; 1971:198-208 (in Japanese)
16. Draganov PV, Wang AY, Othman MO, Fukami N. AGA institute clinical practice update: Endoscopic submucosal dissection in the United States. Clin Gastroenterol Hepatol 2019; 17: 16-25.
17. Akahoshi K, Motomura Y, Kubokawa M, Gibo J, Kinoshita N, Osada S, *et al.* Endoscopic submucosal Dissection for Early Gastric Cancer using the Clutch Cutter: A large single-center experience. Endosc Int Open 2015; 3:E432-E438.
18. Liu L, Liu H, Feng Z. A narrative review of postoperative bleeding in patients with gastric cancer treated with endoscopic submucosal dissection. J Gastrointest Oncol 2022; 13:413-425.
19. Green FW Jr, Kaplan MM, Curtis LE, Levine PH. Effect of acid and pepsin on blood coagulation and platelet aggregation. A possible contributor prolonged gastroduodenal mucosal hemorrhage. Gastroenterology 1978; 74: 38-43.
20. Lin HJ, Lo WC, Lee FY, Perng CL, Tseng GY. A prospective randomized comparative trial showing that omeprazole prevents rebleeding in patients with bleeding peptic ulcer after successful endoscopic therapy. Arch Intern Med 1998; 158: 54-58.
21. Hatlebakk JG. Review article: Gastric acidity--Comparison of esomeprazole with other proton pump inhibitors. Aliment Pharmacol Ther 2003; 17; Suppl 1: 10-15; discussion 16-17.
22. Suzuki H, Takizawa K, Hirasawa T, Takeuchi Y, Ishido K, Hoteya S, *et al.* for J-WEB/EGC group. Short-term outcomes of multicenter prospective cohort study of gastric endoscopic resection: "Real-world evidence" in Japan. Dig Endosc 2019; 31:30-39.
23. Ichida T, Ueyama S, Eto T, Kusano F, Sakai Y. Randomized controlled trial comparing the effects of vonoprazan plus rebamipide and esomeprazole plus rebamipide on gastric ulcer healing induced by endoscopic submucosal dissection. Intern Med 2019; 58:159-166.
24. Bang CS, Shin WG, Seo SI, Choi MH, Jang HJ, Park SW, *et al.* Effect of ilaprazole on the healing of endoscopic submucosal dissection-induced gastric ulcer: Randomized-controlled, multicenter study. Surg Endosc 2019; 33: 1376-1385.