

Dose-related healing of artificial ulcers after endoscopic submucosal dissection using esomeprazole

A randomized controlled study

Jihwan Ko, MD, Su Jin Kim, PhD, MD, Dae Hwan Kang, PhD, MD*, Cheol Woong Choi, PhD, MD, Hyung Wook Kim, PhD, MD, Su Bum Park, PhD, MD

Abstract

Background: Endoscopic submucosal dissection (ESD) is a standard procedure for treating gastric neoplasms. However, ESD causes larger artificial ulcers other than mucosal resection methods. We conducted this prospective randomized controlled study to evaluate the effect of stronger acid suppression on ESD ulcers caused by doubling the proton pump inhibitor (PPI) dose and compare the effects of 20-mg (standard dose) and 40-mg (double dose) esomeprazole (Eswonamp™, Daewon Pharmaceutical Co., Ltd., Seoul, Korea) on ulcer healing.

Methods: One hundred ninety-seven patients who underwent gastric ESD from July 2017 to December 2017 at Pusan National University Yangsan Hospital were enrolled and randomly assigned to the standard or double-dose group. Change in ulcer size from the day of ESD to 4 weeks after ESD and the scar-change rate were compared between the groups.

Results: There were no significant differences in ulcer contraction (84.5% in 20 mg group vs 86.3% in 40 mg group, $P = .91$) or scar-change rate (30.9% vs 30.6%, $P > .99$) between the groups. In a multivariate analysis, initial ulcer size [odds ratio (OR) 0.24; 95% confidence interval (CI) 0.11–0.50] and early gastric cancer (OR 0.22, 95% CI 0.08–0.58) were significantly associated with delayed ulcer healing.

Conclusions: Both 40 and 20-mg esomeprazole have similar effects on ESD-induced ulcer area reduction, suggesting that strong acid suppression does not necessarily result in rapid artificial ulcer healing.

Trial registration number: RCT no.: KCT0002885

Abbreviations: EGC = early gastric cancer, ESD = endoscopic submucosal dissection, PPI = proton pump inhibitor.

Keywords: endoscopic submucosal dissection, esomeprazole, proton pump inhibitor, ulcer healing

Editor: Yan Li.

JK and SJK contributed equally to this work and share first authorship.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

The authors have no funding and conflicts of interest to disclose.

Department of Internal Medicine, Pusan National University School of Medicine and Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan, Korea.

* Correspondence: Dae Hwan Kang, PhD, MD, Department of Internal Medicine, Medical Research Institute, Pusan National University School of Medicine and Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, 20, Geumo-ro, Mulgeum-eup, Yangsan-si, Gyeongsangnam-do 50612, Korea (e-mail: sulsulpul@naver.com).

Copyright © 2019 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Medicine (2019) 98:20(e15701)

Received: 11 July 2018 / Received in final form: 10 December 2018 / Accepted: 23 April 2019

<http://dx.doi.org/10.1097/MD.00000000000015701>

1. Introduction

Recently, endoscopic submucosal dissection (ESD) has become the standard procedure for treating gastric neoplasms, such as gastric adenoma and early gastric cancer (EGC). ESD can achieve a higher *en bloc* resection rate than endoscopic mucosal resection, regardless of the lesion size.^[1] However, the size of the artificial ulcers induced by ESD is large. It is well known that the large resected specimen size is an independent risk factor for delayed bleeding.^[2] To decrease the risk of delayed bleeding, both prophylactic coagulation of visible vessels on the ulcer base and administration of proton pump inhibitors (PPIs) are performed after ESD.

Inhibitors of gastric acid secretion, such as PPIs, have been administered after ESD to induce rapid ulcer healing. Recently, the effects of vonoprazan, a novel potassium-competitive acid blocker, have been evaluated with respect to ESD scars. Several studies have reported that vonoprazan is superior to PPIs for healing artificial ulcers, suggesting that the results may be due to its higher acid-inhibitory effects.^[3–6] However, other studies have shown that there is no significant difference between vonoprazan and PPIs.^[7,8] With respect to PPIs, several studies have reported that a higher dose of PPIs results in higher gastric pH.^[9,10] Previous studies have compared the effectiveness of standard-dose vs half-dose rabeprazole and lansoprazole.^[11,12] Half-dose PPIs showed a comparable effect on artificial ulcer healing to that

of standard-dose PPIs.^[10,11] Thus, it remains unknown whether higher acid suppression using vonoprazan is necessarily associated with a higher ulcer healing rate. Given that vonoprazan is currently not available in all countries, double-dose PPIs can be considered as a replacement for vonoprazan, because the double dose of PPIs showed stronger acid suppression than the standard dose, although its potential is not the same as that of vonoprazan. Thus, the aim of this study was to compare the standard dose of PPIs with the doubled dose of PPIs to extrapolate the effect of vonoprazan on ESD ulcers through stronger acid suppression by doubling the dose of PPIs administered to patients after ESD. Moreover, this prospective randomized controlled study was conducted to evaluate whether artificial ulcer healing after ESD is faster when increasing the dose of the PPI esomeprazole from 20 mg (standard dose) to 40 mg (double dose).

2. Methods

2.1. Patients, randomization, and masking

Patients who underwent ESD for gastric mucosal neoplasms from July 2017 to December 2017 at Pusan National University Yangsan Hospital were eligible for enrollment in this study. During the study period, 200 patients who required gastric ESD for gastric neoplasms were considered for inclusion. Three patients refused to participate. Finally, 197 patients were randomly assigned to the standard-dose (20-mg/day esomeprazole) and double-dose (40-mg/day esomeprazole) groups. Randomization was performed using computer-generated randomization lists. The endoscopists who performed the ESD and follow-up endoscopy were unaware of the patients' treatment group.

Five patients were excluded from the analysis during the study period. Two patients in the standard group did not visit our

hospital after ESD. Therefore, those patients could not be followed up to evaluate ulcer healing after 4 weeks of PPI treatment. One patient in the standard group underwent an additional gastrectomy due to noncurative resection of ESD. In each group, 1 patient developed hematemesis requiring readmission and treatment (endoscopic coagulation and high-dose PPI infusion) and was dropped out of the study. The remaining 192 patients completed the study protocol (Fig. 1).

Patient and lesion characteristics, such as sex, age, initial diagnosis, location of the lesion, endoscopic findings, and body weight, were recorded. Abdominal computed tomography was performed to confirm the absence of perigastric or distant lymph node metastasis in patients with pre-ESD biopsy results indicating adenocarcinoma. This study was approved by the ethics committee of the Institutional Review Board of Pusan National University Yangsan Hospital (RCT no.: KCT0002885), and written informed consent was obtained from all patients before ESD.

2.2. ESD procedure

ESD was performed by 2 skilled endoscopists (CCW and KSJ). Marking dots around the lesion were made using argon plasma coagulation. A fluid mixture (consisting of 10% glycerol and 5% fructose in a normal saline solution) with a small amount of indigo carmine and epinephrine was injected into the submucosa. A round hole was made after grasping the mucosa using a pair of coagulation forceps (Endo Cut Q mode). A circumferential incision into the mucosa was made using an insulation-tipped (IT) diathermic knife (KD-610L; Olympus Optical Co, Ltd, Tokyo, Japan) after inserting the insulated tip into the round hole. Direct dissection of the submucosal layer was carried out with an IT knife. A high-frequency generator (VIO 300D, ERBE Elektromedizin Ltd., Tübingen, Germany) was used for marking, gastric mucosa incision, and gastric submucosa dissection.

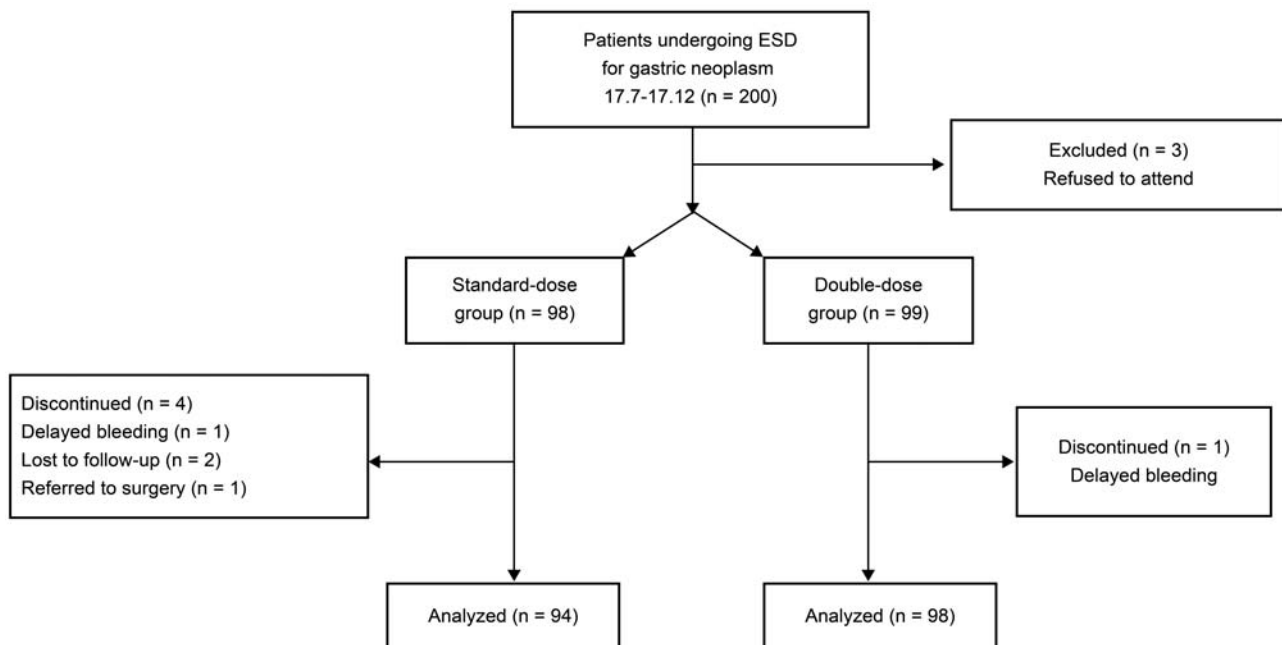


Figure 1. Flow chart of the participants. ESD=endoscopic submucosal dissection.

2.3. Evaluations after 4 weeks

All patients were administered either 20 or 40 mg of esomeprazole daily starting on the morning when ESD was performed. Patients were allowed oral intake after second-look endoscopy the next day, unless serious complications occurred. Follow-up endoscopy was performed at 4 weeks after ESD. Artificial ulcers were evaluated using photographs taken from the same view as those taken immediately after ESD. The dimensions of the initial ulcer were measured from the pathologic specimen, and the dimensions of the ulcer after 4 weeks were measured using biopsy forceps. The ulcer contraction rate was assessed by calculating the percent reduction in size from the initial ulcer size after ESD [(initial ulcer size – ulcer size after 4 weeks/initial ulcer size) × 100]. The size of the ulcer was calculated using the following formula: initial ulcer size = $\pi(R/2)^2$ (measured using the pathology specimen), and ulcer after 4 weeks = $\pi(r/2)^2$ (measured using forceps) (Fig. 2).

2.4. Statistical analysis

Statistical comparisons between the 2 groups were performed using the Student *t*-test, and the correlations between the ulcer contraction rate and drug dose per body weight were determined using a linear regression analysis. Factors associated with scar change were analyzed using a logistic regression analysis. The correlations between drug dose (20 and 40 mg) and the scar change rate were analyzed using Fisher’s exact test. *P* < .05 was considered statistically significant. Statistical analyses were performed using SPSS (version 21, IBM Corp., Armonk, NY).

3. Results

3.1. Baseline characteristics

A total of 192 patients were randomly assigned to the standard- and double-dose groups and completed the study protocol. There

Table 1

Baseline data of the treatment groups.

| | | Esomeprazole dose | | P value |
|----------------------|----------------|-------------------|-----------------|---------|
| | | 20 mg (n=94) | 40 mg (n=98) | |
| Sex | Male | 71 (75.5) | 71 (72.4) | .742 |
| | Female | 23 (24.5) | 27 (27.6) | |
| Antiplatelet drug+ | Yes | 14 (14.9) | 15 (15.3) | 1.000 |
| | No | 80 (85.1) | 83 (84.7) | |
| Location | U | 7 (7.4) | 1 (1.0) | .141 |
| | M | 16 (17.0) | 18 (18.4) | |
| | L | 71 (75.5) | 79 (80.6) | |
| Pathology | LGD | 61 (64.9) | 54 (55.1) | .130 |
| | HGD | 3 (3.2) | 2 (2.0) | |
| | Adenocarcinoma | 27 (28.7) | 37 (37.8) | |
| | Other | 3 (3.2)* | 5 (5.1)** | |
| Adenocarcinoma Depth | Mucosa | 25 (26.6) | 35 (35.4) | 1.000 |
| | Submucosa | 2 (2.1) | 2 (2.0) | |
| Differentiation | Well | 23 (24.2) | 26 (26.5) | .510 |
| | Moderate | 5 (5.3) | 9 (9.1) | |
| | Poor | 0 (0.0) | 1 (1.0) | |

+Aspirin, clopidogrel.

* Lipoma (n=1), gastritis (n=2)

** Gastritis 4, neuroendocrine tumor 1

HGD = high-grade dysplasia, L = lower, LGD = low-grade dysplasia, M = middle, U = upper.

were 115 low-grade dysplasia cases, 5 high-grade dysplasia cases, 64 EGC cases, 1 lipoma case, and 2 gastritis cases treated by ESD. Baseline characteristics were not significantly different between the treatment groups (Table 1). One patient in each group underwent ESD without discontinuing the dual antiplatelet therapy (aspirin and clopidogrel) because of a high cardiovascular risk. In most situations when the patient required antiplatelet therapy, such as if they had previously undergone cardiovascular stent insertion, the patients were only administered aspirin without clopidogrel.

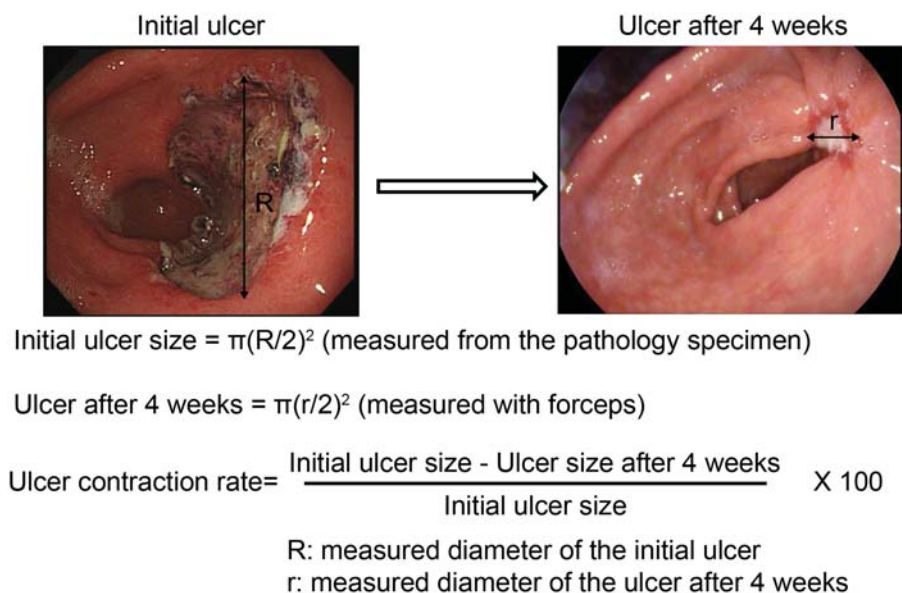


Figure 2. Measurement of the ulcer size and calculation of the ulcer contraction rate.

Table 2
Comparison of ulcer contraction and scar change rates.

| | Esomeprazole dose | | P value |
|---------------------------------------|-------------------|---------------|---------|
| | 20 mg (n=94) | 40 mg (n=98) | |
| Ulcer contraction rate (mean ± SD) | 86.45 ± 11.10 | 86.27 ± 11.01 | 0.907 |
| Scar change | | | |
| No | 65 (69.1) | 68 (69.4) | 1.000 |
| Yes | 29 (30.9) | 30 (30.6) | |

SD = standard deviation.

3.2. Comparison of the PPI dose effect between the groups

The ulcer contraction rate (86.5% in the 20-mg group vs 86.3% in the 40-mg group, $P=.91$) or scar-change rate (30.9% vs 30.6%, $P>.99$) were not significantly different between the groups (Table 2). In a univariate analysis, initial ulcer size, antiplatelet drug use, and EGC were associated with delayed ulcer healing. A multivariate analysis showed that the initial ulcer size [odds ratio (OR) 0.24; 95% confidence interval (CI) 0.11–0.50] and EGC as the final pathologic result (OR 0.22; 95% CI 0.08–0.58) were independent risk factors associated with delayed scar changes in artificial ulcers (Table 3).

4. Discussion

Pepsin activity, an important attacking factor for the gastric mucosa, is pH dependent. Therefore, a reduction in gastric acidity could accelerate the healing of gastric ulcers. Several studies have reported that PPIs were more effective than histamine-2 receptor agonist in healing ulcers and preventing delayed bleeding due to the higher acid suppression efficacy of PPI than histamine-2 receptor agonist.^[13,14] Therefore, PPIs are commonly used to prevent bleeding and promote ulcer healing after ESD.^[15,16]

In this study, the scar change and ulcer contraction rates of ESD ulcers on day 28 were not statistically different between patients administered 20 mg and those administered 40 mg of

esomeprazole. In a previous study evaluating acid inhibition according to esomeprazole dose, 40-mg esomeprazole showed stronger acid inhibition compared to 20-mg esomeprazole.^[9] Therefore, our results suggest that stronger acid suppression does not guarantee faster artificial ulcer healing. Several other studies have reported that the rate of artificial ulcer healing was not significantly different between treatment with half doses of PPIs (lansoprazole and rabeprazole) and that with usual doses of PPIs.^[11,12] A study showed that vonoprazan, a novel oral strong acid blocker approved in Japan, was not significantly different than 30-mg lansoprazole for artificial ulcer healing after ESD.^[6] On the other hand, recent studies on vonoprazan have shown that it was superior to the usual dose of 20-mg rabeprazole or 20-mg esomeprazole for ESD-induced ulcer healing.^[4,5] Several studies report faster artificial ulcer healing with vonoprazan, suggesting that strong acid suppression may result in this difference.^[3–6]

A possible reason for the inconsistent results is as follows. The factors influencing the artificial ulcer healing process are different from those influencing the healing of peptic ulcers. Fibrosis from peptic ulcers caused by chronic inflammation inhibits blood flow and mucosal regeneration. In contrast, the increased blood flow at the margin of the artificial ulcer may promote ulcer healing. A well-conditioned environment to promote faster ulcer healing may decrease the differences in the effects of various acid suppressors.

In this study, specimen size was an independent risk factor for delayed scar changes in artificial ulcers. Several studies have reported that a large resected specimen was a risk factor for delayed bleeding.^[2,17] Moreover, another recent study showed that initial ulcer size and ulcer location are independent risk factors for delayed ulcer healing.^[18] Our results also support those results, because an unhealed artificial ulcer was the main cause of delayed bleeding. Another risk factor for delayed scar change in an artificial ulcer was adenocarcinoma as the underlying pathology. The specimen size required to resect EGC lesions tended to be larger than that required for other pathologic results. A minimum of 2-mm distance from the lesion to the margin of the specimen is needed to achieve curative resection for EGC, because ESD specimens are examined by serial

Table 3
Results of the univariate and multivariate analyses of factors associated with delayed scar change.

| | Univariate | | Multivariate | |
|---------------------------|------------|-------------------|--------------|-------------------|
| | P value | OR (95% CI) | P value | OR (95% CI) |
| Dose/weight ratio (mg/kg) | .189 | 3.13 (0.57–17.19) | | |
| Initial ulcer size (cm) | <.001 | 0.28 (0.17–0.48) | <.001 | 0.24 (0.11–0.50) |
| Diabetes mellitus | .118 | 0.44 (0.16–1.23) | | |
| Esomeprazole dose | | | | |
| 20 mg | .971 | 1 (Reference) | | |
| 40 mg | | 0.99 (0.54–1.83) | | |
| Antiplatelet drug use+ | .040 | 0.31 (0.10–0.95) | .403 | 0.58 (0.17–2.06) |
| Initial ulcer size ≥4 cm | .020 | 0.31 (0.11–0.83) | .136 | 3.25 (0.69–15.23) |
| Position | | | | |
| L | | 1 (Reference) | | |
| M | .856 | 0.85 (0.15–4.83) | | |
| U | .962 | 0.96 (0.15–6.04) | | |
| Pathology | | | | |
| Other | <.001 | 1 (Reference) | .002 | 1 (Reference) |
| Adenocarcinoma | | 0.14 (0.06–0.34) | | 0.22 (0.08–0.58) |

+Aspirin, clopidogrel.

*Low-grade dysplasia, high-grade dysplasia, lipoma, gastritis, and neuroendocrine tumor. CI = confidence interval, L = lower, M = middle, OR = odds ratio, U = upper.

sections at 2-mm intervals. Leaving enough margin to achieve a curative resection for EGC can result in a large ulcer size, and might be the reason for the delayed scar changes in artificial ulcers in patients with EGC.

Delayed ulcer healing can increase the risk of post-ESD bleeding. The bleeding can result in hypovolemic shock and severe anemia. Therefore, an effort to promote artificial ulcer healing is important to reduce the risk of delayed bleeding. If the size of the ulcer after ESD is larger than expected, the combination of an acid-suppression agent and a cytoprotective agent could provide a beneficial effect greater than that of strong acid suppression in the healing process of artificial ulcers.^[19]

This study has some limitations. First, the study was conducted at a single center. Second, the number of patients with large ulcers was too small to confirm that there was no difference in the efficacy for ulcer healing between the 2 groups. In the future, a head-to-head, multicenter, randomized controlled study comparing half, standard, and double-dose PPIs and vonoprazan needs to be conducted, which might help in determining the most cost-effective drug and dose.

A 40-mg dose of esomeprazole has an effect on ESD-induced ulcer area reduction similar to that of a 20-mg dose. This result suggests that strong acid suppression does not necessarily result in rapid artificial ulcer healing.

Author contributions

Conceptualization: Jihwan Ko, Dae Hwan Kang.

Data curation: Jihwan Ko.

Formal analysis: Jihwan Ko.

Funding acquisition: Dae Hwan Kang.

Investigation: Su Jin Kim, Cheol Woong Choi.

Methodology: Cheol Woong Choi.

Project administration: Dae Hwan Kang.

Resources: Hyung Wook Kim.

Supervision: Su Jin Kim.

Validation: Su Bum Park.

Visualization: Jihwan Ko.

Writing – review & editing: Su Jin Kim.

Dae Hwan Kang orcid: 0000-0002-7539-0723.

References

- [1] Tanaka M, Ono H, Hasuie N, et al. Endoscopic submucosal dissection of early gastric cancer. *Digestion* 2008;77:23–8.
- [2] Kim SJ, Choi CW, Kang DH, et al. Second-look endoscopy and factors associated with delayed bleeding after endoscopic submucosal dissection. *World J Gastrointest Endosc* 2016;8:173–9.
- [3] 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;42:719–30.
- [4] Maruoka M, 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.
- [5] Yamasaki A, Yoshio T, Muramatsu Y, et al. Vonoprazan is superior to rabeprazole for healing endoscopic submucosal dissection: induced ulcers. *Digestion* 2018;97:170–6.
- [6] 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;8:716–22.
- [7] Ishii Y, Yamada H, Sato T, et al. Effects of vonoprazan compared with esomeprazole on the healing of artificial postendoscopic submucosal dissection ulcers: a prospective, multicenter, two-arm, randomized controlled trial. *Gastroenterol Res Prac* 2018;2018:1615092.
- [8] Hirai A, Takeuchi T, Takahashi Y, et al. Comparison of the effects of vonoprazan and lansoprazole for treating endoscopic submucosal dissection-induced artificial ulcers. *Dig Dis Sci* 2018;63:974–81.
- [9] Jungghard O, Hassan-Alin M, Hasselgren G. The effect of the area under the plasma concentration vs time curve and the maximum plasma concentration of esomeprazole on intragastric pH. *Eur J Clin Pharmacol* 2002;58:453–8.
- [10] Wilder-Smith C, Röhss K, Bokelund Singh S, et al. The effects of dose and timing of esomeprazole administration on 24-h, daytime and night-time acid inhibition in healthy volunteers. *Aliment Pharmacol Ther* 2010;32:1249–56.
- [11] Kawano S, Okada H, Kawahara Y, et al. Proton pump inhibitor dose-related healing rate of artificial ulcers after endoscopic submucosal dissection: a prospective randomized controlled trial. *Digestion* 2011;84:46–53.
- [12] Park HJ, Kim HS, Kim BR, et al. Half-dose rabeprazole has an equal efficacy to standard-dose rabeprazole on endoscopic submucosal dissection-induced ulcer. *Dig Dis Sci* 2013;58:1054–61.
- [13] Ye BD, Cheon JH, Choi KD, et al. Omeprazole may be superior to famotidine in the management of iatrogenic ulcer after endoscopic mucosal resection: a prospective randomized controlled trial. *Aliment Pharmacol Ther* 2006;24:837–43.
- [14] 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;84:315–20.
- [15] Tomita T, Kim Y, Yamasaki T, et al. Prospective randomized controlled trial to compare the effects of omeprazole and famotidine in preventing delayed bleeding and promoting ulcer healing after endoscopic submucosal dissection. *J Gastroenterol Hepatol* 2012;27:1441–6.
- [16] Yamaguchi Y, Katsumi N, Tauchi M, et al. A prospective randomized trial of either famotidine or omeprazole for the prevention of bleeding after endoscopic mucosal resection and the healing of endoscopic mucosal resection-induced ulceration. *Aliment Pharmacol Ther* 2005;21:111–5.
- [17] Libânio D, Costa MN, Pimentel-Nunes P, et al. Risk factors for bleeding after gastric endoscopic submucosal dissection: a systematic review and meta-analysis. *Gastrointest Endosc* 2016;84:572–86.
- [18] Shimozato A, Sasaki M, Ogasawara N, et al. Risk factors for delayed ulcer healing after endoscopic submucosal dissection of gastric neoplasms. *J Gastrointest Liver Dis* 2017;26:363–8.
- [19] Mózsik G, Hunyady B, Garamszegi M, et al. Dynamism of cytoprotective and antisecretory drugs in patients with unhealed gastric and duodenal ulcers. *J Gastroenterol Hepatol* 1994;9:S88–92.