



# Effects of preoperative proton pump inhibitor administration on bleeding after gastric endoscopic submucosal dissection: A systematic review and meta-analysis

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## Abstract

**Background and aim:** The efficacy of using proton pump inhibitors (PPIs) prior to gastric endoscopic submucosal dissection (ESD) to reduce gastric bleeding remains controversial. This study aimed to systematically review the literature to evaluate the efficacy of preoperative PPI use to reduce post-ESD bleeding.

**Methods:** PubMed, the Cochrane library, and the Igaku-Chuo-Zasshi database were searched to identify randomized trials eligible for inclusion in the systematic review. Data from four studies (406 patients) were combined to calculate a pooled risk difference (RD) for developing post-ESD bleeding.

**Results:** Compared with patients who received no premedication, the pooled RD for post-ESD bleeding in patients who received preoperative PPI was  $-0.027$  (95% confidence interval:  $-0.070$ – $0.017$ ,  $p = 0.228$ ), without significant heterogeneity. Preoperative PPI use significantly increased gastric pH (weighted mean difference:  $1.289$ , 95% CI:  $0.227$ – $2.352$ ,  $p = 0.0174$ ).

**Conclusions:** This systematic review and meta-analysis showed that premedication with PPI had no advantage for the prevention of post-ESD bleeding, despite increasing gastric pH.

## Keywords

Proton pump inhibitor, premedication, systematic review, gastric endoscopic submucosal dissection, gastric bleeding

Received: 13 January 2015; accepted: 29 April 2015

## Introduction

Endoscopic submucosal dissection (ESD) was developed in Japan as an advanced endoscopic resection technique for early gastric cancer.<sup>1,2</sup> Although ESD is considered safe, bleeding is still a common complication.<sup>3,4</sup> A meta-analysis in 2011 showed that proton pump inhibitors (PPIs) prevented bleeding due to ESD-induced gastric ulcers more effectively than histamine H<sup>2</sup>-receptor antagonists.<sup>5</sup> However, delayed bleeding occurs in approximately 5% of patients who undergo gastric ESD.<sup>6</sup>

PPIs produce a high gastric pH by irreversibly binding to the proton pumps on gastric parietal cells.<sup>7</sup> The optimal time for the full effect of PPIs is reported to be several days.<sup>8</sup> Several randomized controlled trials (RCTs) evaluated the efficacy of PPI administration before ESD. Watanabe et al. reported that preoperative PPI administration was useful for preventing post-ESD bleeding.<sup>9</sup> However, other studies showed that

premedication did not influence post-ESD bleeding rates.<sup>10–12</sup> We proposed that systematically pooling data from all published reports might provide a better understanding of the efficacy of preoperative PPI use for preventing post-ESD bleeding. Our objective was to perform a systematic review and meta-analysis of RCTs

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comparing the impact of no premedication versus preoperative PPI use on post-ESD bleeding.

## Methods

Before performing the meta-analysis, we developed a protocol to detail search strategies, study selection criteria, methods for relevant data extraction, quality assessment, and statistical analysis.

### Search strategy

PubMed, the Cochrane library, and the Igaku-Chuo-Zasshi database in Japan (from 1950 to December 2014) were used to perform a systematic literature search. A combination of the following words was used for the search: (endoscopic submucosal dissection OR endoscopic mucosal resection) AND (proton pump inhibitor). Articles published in any language were included.

### Inclusion and exclusion criteria

Studies meeting the following inclusion criteria were considered eligible: (1) study type: RCT; (2) population: patients who underwent gastric ESD; (3) intervention: PPI use from the day before ESD or earlier; (4) comparator: no PPI before the day of ESD; (5) outcome: post-ESD bleeding. Duplicate publications, reviews, and conference abstracts were excluded.

### Outcome measures

The primary outcome of this study was clinical evidence of bleeding after ESD. Post-ESD bleeding included hematemesis, melena, reduced hemoglobin count by more than 2 g/dl, or endoscopically evident bleeding. The secondary outcome was gastric pH.

### Data extraction

Standardized data abstraction sheets were prepared. Extracted data included study design, study quality, intervention, and outcomes. All articles were independently examined for eligibility by two reviewers (TN and TA). Disagreements were resolved by consulting a third reviewer (HS). We contacted the corresponding authors in order to clarify detail of studies.

### Assessment of methodological quality

The methodological quality of each study was assessed using the risk-of-bias tool outlined in the Cochrane Handbook for Systematic Reviews of Interventions

(version 5.1.0). Two reviewers (TN and HS) reviewed all studies and assessed six key RCT quality influencers: sequence generation, allocation concealment, blinding of participants and outcome assessors, management of incomplete outcome data, completeness of outcome reporting, and other potential threats to validity.

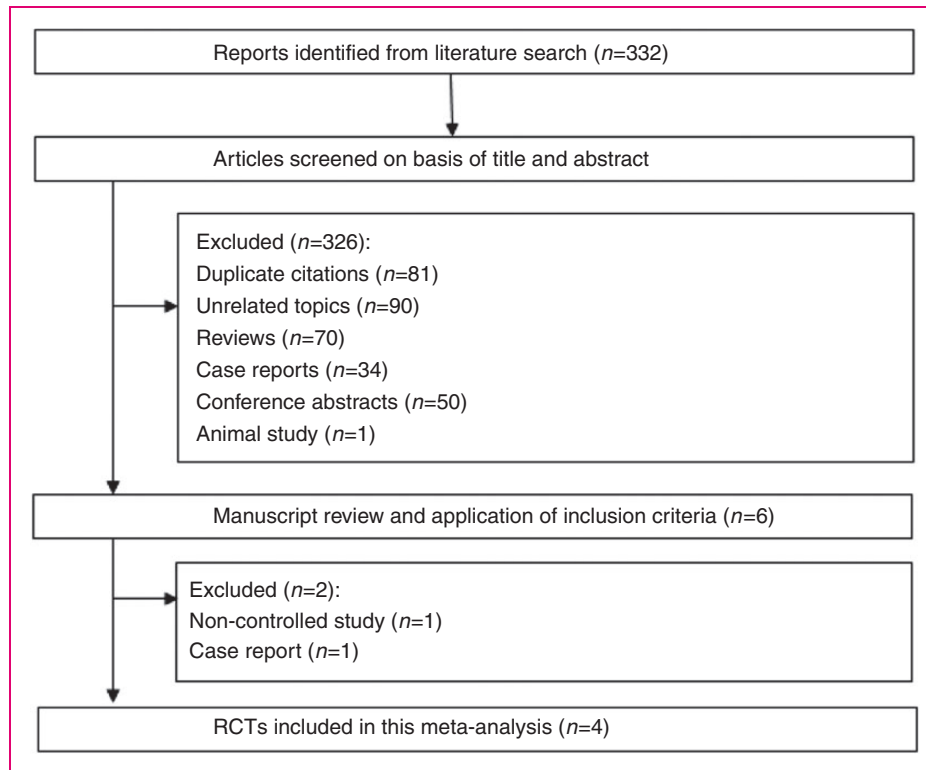
### Statistical analysis

Data were entered into the StatsDirect statistical package (StatsDirect Ltd., Cheshire, UK). Separate analyses were performed for each outcome using a risk difference (RD) or weighted mean difference (WMD). We used a random-effect model to calculate summary RDs and 95% confidence intervals (CIs). We always used a random-effect model, regardless of the significance of the heterogeneity. Heterogeneity between studies was assessed by Cochran's  $Q$  and  $I^2$  tests. Because of the low power of the  $Q$  test, a cut-off value ( $<0.10$ ) was used to reject homogeneity, which thereby indicated heterogeneity.<sup>13</sup> An  $I^2$  score of  $\geq 50\%$  indicates more than moderate heterogeneity. Some trials reported medians as the measure of treatment effect, with an accompanying interquartile range. For the purpose of analysis, medians were assumed to be equivalent to means, and standard deviation (SD) was estimated from interquartile ranges as follows:  $SD = \text{interquartile range} \times 0.74$ .<sup>14,15</sup> In all trials, PPIs were administered on the day of ESD either before or immediately after ESD. Therefore, all eligible trials were grouped into pre- and post-ESD groups and subgroup analysis was also performed. An analysis of sensitivity was performed in order to evaluate the stability of the results. Finally, we used funnel plot asymmetry to detect any publication bias in the meta-analysis and Egger's regression test to measure funnel plot asymmetry.

## Results

### Search results

Our database search yielded a total of 332 citations (Figure 1). After adjusting for duplicates, 251 studies remained. Of these, 245 studies were removed from consideration after abstract review based on the exclusion criteria (90 unrelated topics, 70 reviews, 34 case reports, 50 conference abstracts, and one animal study). The remaining six studies were examined in detail. Another two studies were then excluded (one lack of control<sup>16</sup> and one case report<sup>17</sup>). Finally, four studies were included in the systematic review and meta-analysis (Clinical trials registration number: Baeg et al.; NCT00844675, Hikichi et al.; UMIN000011487). The characteristics of these studies



**Figure 1.** Flow of RCTs included in the systematic review.

are summarized in Table 1. The indication for ESD was early gastric cancer or adenoma in all four RCTs.

### Quality assessment

The risks of bias in the included RCTs are shown in Table 2. In general, the included RCTs were at low risk of bias for most of the aspects evaluated. All four RCTs described the specific methods used for random sequence generation, and one RCT did not perform allocation concealment. In three RCTs, blinding of participants and outcomes assessment were not performed. One RCT did not adequately assess incomplete outcomes. Avoidance of selective outcome reporting was found in all four RCTs. All four RCTs were free of other biases.

### Meta-analysis results

When data were pooled, post-ESD bleeding was reported in nine of 201 patients (4.5%) who received preoperative PPIs and in 13 of 205 patients (6.3%) who did not receive premedication (RD  $-0.027$ , 95% CI:  $-0.070$ – $0.017$ ,  $p=0.228$ ) (Figure 2, Table 1). There was no significant heterogeneity among the trial results ( $I^2=0\%$ ,  $p=0.63$ ). The sensitivity analysis performed using sequential excluding of one trial at a time did not alter the results. The Egger test suggested no significant

funnel plot asymmetry ( $p=0.70$ ), indicating no evidence of substantial publication bias.

Gastric pH was recorded in all four studies. Baeg et al. reported the mean intragastric pH monitored for 48 h after ESD,<sup>11</sup> while gastric juice was collected during ESD in the other studies. Since the number of reports was limited, data obtained using the different measurement methods were combined in the present meta-analysis. Compared with no premedication, preoperative PPI use significantly increased gastric pH (WMD: 1.289, 95% CI: 0.227–2.352,  $p=0.0174$ , Figure 3). However, there was significant heterogeneity among the trial results ( $I^2=91.3\%$ ,  $p<0.0001$ ). Watanabe et al.<sup>9</sup> and Ono et al.<sup>10</sup> administered PPI after ESD on the day of the ESD (post-ESD group), while Baeg et al.<sup>11</sup> and Hikichi et al.<sup>12</sup> administered PPI before ESD on the day of the ESD (pre-ESD group). Subgroup analysis indicated a significantly higher gastric pH with preoperative PPI use compared with no premedication for both the pre- and post-ESD groups, and the heterogeneity disappeared ( $p=0.43$  and  $p=0.17$ , respectively). The WMD in the post-ESD group (2.171, 95% CI: 1.548–2.794,  $p<0.0001$ ) was higher than that in the pre-ESD group (0.598, 95% CI: 0.182–1.015,  $p=0.0049$ ). Sensitivity analysis omitting the study that used 48-hour intragastric pH monitoring did not alter the findings.

**Table 1.** Characteristics of studies included in the systematic review

Author Year	Country	Premedication	PPI administration of ESD day	Follow-up endoscopy	Patients number	Age $\pm$ SD	Gender M/F	Post-ESD bleeding (%)	Gastric pH measurement	Mean pH $\pm$ SD
Watanabe 2006	Japan	LPZ 30 mg o.d. 7 days before ESD	Oral LPZ 30 mg	day 7, 56	51	72.5 $\pm$ 9.1	37/14	0 (0%)	Collecting gastric juice	7.5 $\pm$ 0.7
		No treatment	Oral LPZ 30 mg after ESD		47	70.1 $\pm$ 8.0	37/10	3 (6.4%)	during ESD	5.1 $\pm$ 1.4
Ono 2009	Japan	OPZ 20 mg o.d. 1 day before ESD	iv OPZ 20 mg before and after ESD	day 1, 7, 28	81	70.5 $\pm$ 8.3	51/30	6 (7.4%)	Collecting gastric juice	7.3 $\pm$ 0.6
		No treatment	iv OPZ 20 mg after ESD		74	70.2 $\pm$ 9.1	60/14	6 (8.1%)	during ESD	5.6 $\pm$ 3.7
Baeg 2014	Korea	RPZ 20 mg b.i.d. 5 days before ESD	iv PPZ 40 mg 2h before ESD	day 1, 30	45	59 $\pm$ 8.9	24/21	3 (6.7%)	48-h pH monitoring	6.7 $\pm$ 1.7
		Placebo	iv PPZ 40 mg 2h before ESD		53	58 $\pm$ 10	42/11	3 (5.7%)	after ESD	6.5 $\pm$ 1.3
Hikichi 2014	Japan	RPZ 20 mg o.d. 3 days before ESD	oral RPZ 20 mg	day 7, 56	24	73.3 $\pm$ 7.8	18/6	0 (0%)	Collecting gastric juice	7.2 $\pm$ 0.6
		No treatment	oral RPZ 20 mg 7-8 h before ESD		31	70.4 $\pm$ 9.0	21/10	1 (3.2%)	during ESD	6.5 $\pm$ 1.1

ESD: endoscopic submucosal dissection; PPI: proton pump inhibitor, LPZ: lansoprazole, OPZ: omeprazole, PPZ: pantprazole, RPZ: rabeprazole; iv: intravenous.

Follow-up endoscopy: the days after the ESD.

**Table 2.** Evaluation of bias of RCTs included in the systematic review

First author	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Adequate assessment of incomplete outcome	Selective reporting avoided	No other bias
Watanabe	Yes	Yes	No	No	Yes	Yes	Yes
Ono	Yes	Yes	No	No	Yes	Yes	Yes
Baeg	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hikichi	Yes	No	No	No	No	Yes	Yes

Yes: Low risk of bias.

No: High risk of bias.

Unclear: Unclear risk of bias.

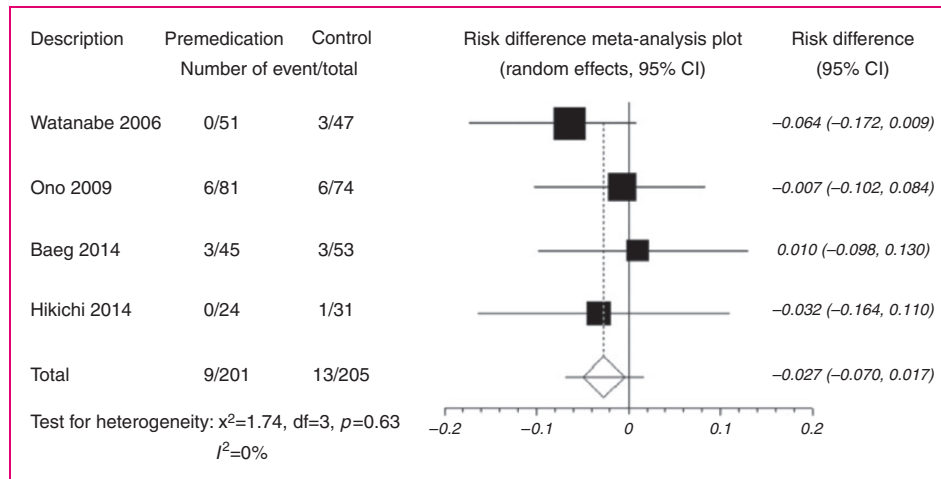
## Discussion

This systematic review and meta-analysis indicates that preoperative PPI use significantly increases gastric pH but confers no advantage for preventing post-ESD bleeding.

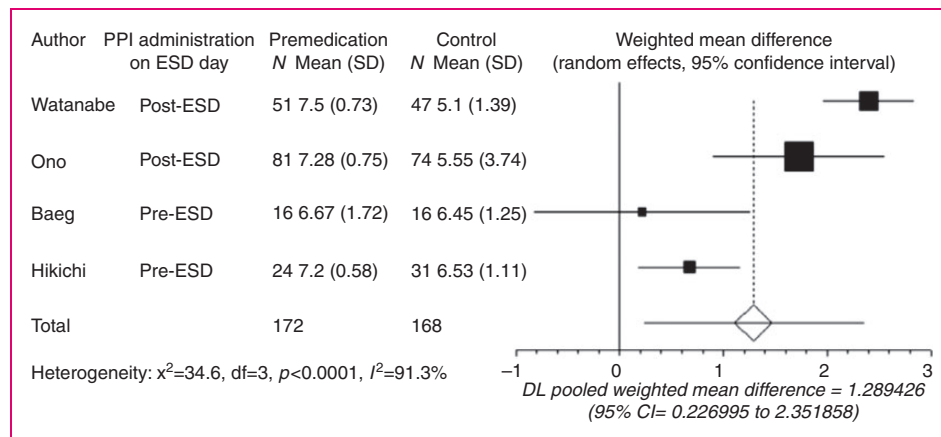
Ozawa et al. reported intragastric pH monitoring in *H. pylori*-positive patients treated with H<sup>2</sup>-receptor antagonist or PPI. The mean pH was 6.9  $\pm$  0.3 in patients treated with PPI, and it was 4.3  $\pm$  0.7 in patients treated with H<sup>2</sup>-receptor antagonist.<sup>18</sup> In order to control bleeding, PPIs should be administered instead of H<sup>2</sup>-receptor antagonist after ESD.

Platelet aggregation is reduced to less than 50% at a pH of 6.4 or lower. When the pH falls below 5.4, platelet aggregation and plasma coagulation are virtually abolished. Below pH 4.0, fibrin clots are dissolved.<sup>19,20</sup> Therefore, gastric pH must be kept >5.4 to prevent bleeding.

The mean gastric pH in patients who did not receive premedication in all four RCTs was relatively high (5.9  $\pm$  2.5; 5.1–6.5). This might be because most patients with gastric neoplasms have atrophic gastritis. As corpus atrophy results in a reduced number of acid-producing parietal cells, the stomach becomes hypochlorhydric. The reduced number of parietal cells



**Figure 2.** Forest plot displaying the risk difference and 95% CIs of each study for post-ESD bleeding. Premedication, preoperative PPI use; Control, no premedication



**Figure 3.** Forest plot displaying the weighted mean difference and 95% CIs of each study for gastric pH. Premedication, preoperative PPI use; Control, no premedication; Post-ESD, PPI administration on ESD day was post-operative; Pre-ESD, PPI administration on ESD day was preoperative.

would require a lower PPI dose in order to be fully inhibited, resulting in no clinically significant difference in post-ESD bleeding rates between preoperative PPI use and no premedication.

This systematic review has several limitations that should be taken into account. Most study participants were Japanese and Korean, so the results may not be generalizable to other races. Although the outcome parameter is rather objective (hematemesis, melena, etc), the risk of bias imposed by lacking blinding in three RCTs must be considered. The different time of follow-up endoscopy in the four RCTs may be considered as a source of heterogeneity. Due to the limited number of eligible studies, this study may be statistically underpowered. Patients who took antiplatelet or antithrombotic drugs perioperatively were excluded

from three RCTs, and antiplatelet medication was stopped from 7 days before ESD to 7 days after ESD in one RCT. Three RCTs excluded patients with a high risk of bleeding, such as those who had chronic renal failure or liver cirrhosis. In patients with a high risk of bleeding, intensive acid inhibition by preoperative PPI use might be effective. Further studies with large numbers of patients are warranted to clarify the efficacy of PPI administration before ESD.

In conclusion, premedication with PPI had no advantage for the prevention of post-ESD bleeding, despite increasing gastric pH.

#### Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## Conflicts of interest

During the last 2 years, Author H.S. received scholarship funds for the research from Astellas Pharm Inc., Astra-Zeneca K.K., Otsuka Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., and Zeria Pharmaceutical Co., Ltd. and received service honoraria from Astellas Pharm Inc., Astra-Zeneca K.K., Eisai Co., Otsuka Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., and Zeria Pharmaceutical Co., Ltd. Author T.K. received scholarship funds for the research from Astellas Pharm Inc., Astra-Zeneca K.K., Otsuka Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Eisai Pharmaceutical Co., Ltd., Zeria Pharmaceutical Co., Ltd., Tanabe Mitsubishi Pharmaceutical Co., Ltd. JIMRO Co., Ltd., Kyorin Pharmaceutical Co. Ltd., and received service honoraria from Astellas Pharm Inc., Eisai Pharmaceutical Co., Ltd., JIMRO Co., Ltd., Tanabe Mitsubidhi Pharmaceutical Co. Ltd., Otsuka Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Miyarisan Pharmaceutical Co. Ltd., and Zeria Pharmaceutical Co., Ltd. Author N.Y. received scholarship funds for the research from Astra-Zeneca K.K., Takeda Pharmaceutical Co., Ltd., Eisai Co., Top Corporation, Kaigen Pharm Co., Ltd., ASKA Pharmaceutical Co., Ltd., FUJIFILM Corporation, Boston Scientific Japan K.K., Century Medical Inc., and Covidien Japan Inc. The funding source had no role in the design, practice or analysis of this study. There are no other conflicts of Interests for this article.

## References

- Kodashima S, Fujishiro M, Yahagi N, et al. Endoscopic submucosal dissection using flexknife. *J Clin Gastroenterol* 2006; 40: 378–384.
- Uraoka T, Parra-Blanco A and Yahagi N. Colorectal endoscopic submucosal dissection in Japan and Western countries. *Dig Endosc* 2012; 24(Suppl 1): 80–83.
- Fujishiro M, Chiu PW and Wang HP. Role of antisecretory agents for gastric endoscopic submucosal dissection. *Dig Endosc* 2013; 25(Suppl 1): 86–93.
- Nishizawa T, Suzuki H, Kinoshita S, et al. Second-look endoscopy after endoscopic submucosal dissection for gastric neoplasms: A systematic review. *Dig Endosc* 2015; 27: 279–284.
- Yang Z, Wu Q, Liu Z, Wu K, 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.
- 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.
- Sachs G, Shin JM, Briving C, et al. The pharmacology of the gastric acid pump: The H<sup>+</sup>,K<sup>+</sup> ATPase. *Annu Rev Pharmacol Toxicol* 1995; 35: 277–305.
- Jansen JB, Lundborg P, Baak LC, et al. Effect of single and repeated intravenous doses of omeprazole on pentagastrin stimulated gastric acid secretion and pharmacokinetics in man. *Gut* 1988; 29: 75–80.
- Watanabe Y, Kato N, Maehata T, et al. Safer endoscopic gastric mucosal resection: Preoperative proton pump inhibitor administration. *J Gastroenterol Hepatol* 2006; 21: 1675–1680.
- 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.
- Baeg MK, Choi MG, Moon SJ, et al. Preprocedural rabeprazole treatment before endoscopic submucosal dissection for gastric neoplasms. *Dig Dis Sci* 2014; 59: 2243–2248.
- Hikichi T, Sato M, Watanabe K, et al. Oral rabeprazole administration on a procedure day suppresses bleeding after endoscopic submucosal dissection for gastric neoplasms. *Fukushima J Med Sci* 2014; 60: 68–74.
- Nishizawa T, Suzuki H, Kanai T, et al. Proton pump inhibitor alone vs proton pump inhibitor plus mucosal protective agents for endoscopic submucosal dissection-induced ulcer: A systematic review. *J Clin Biochem Nutr* 2015; 56: 85–90.
- Fraser GL, Devlin JW, Worby CP, et al. Benzodiazepine versus nonbenzodiazepine-based sedation for mechanically ventilated, critically ill adults: A systematic review and meta-analysis of randomized trials. *Crit Care Med* 2013; 41(9 Suppl 1): S30–S38.
- Nishizawa T, Suzuki H, Sagara S, et al. Dexmedetomidine versus midazolam for gastrointestinal endoscopy: A meta-analysis. *Dig Endosc* 2015; 27: 8–15.
- Niimi K, Fujishiro M, Goto O, 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.
- Kurosawa M, Ishibashi K, Iizuka Y, et al. Prevention of delayed bleeding after gastric endoscopic mucosal resection; pretreatment with omeprazole. *J Aizu General Hospital* 1999; 15: 29–31.
- Ozawa T, Yoshikawa N, Tomita T, et al. The influence of feeding on gastric acid suppression in *Helicobacter pylori*-positive patients treated with a proton pump inhibitor or an H<sub>2</sub>-receptor antagonist after bleeding from a gastric ulcer. *J Gastroenterol* 2003; 38: 844–848.
- Green FW Jr., Kaplan MM, Curtis LE, et al. Effect of acid and pepsin on blood coagulation and platelet aggregation. A possible contributor prolonged gastroduodenal mucosal hemorrhage. *Gastroenterology* 1978; 74: 38–43.
- Sugimoto M, Jang JS, Yoshizawa Y, et al. Proton pump inhibitor therapy before and after endoscopic submucosal dissection: A review. *Diagn Ther Endosc* 2012; 2012: 791873.