

# Effect of proton pump inhibitors compared to histamine-2 receptor antagonists on bleeding management and wound healing after endoscopic mucosal resection or endoscopic submucosal dissection: A meta-analysis of randomized clinical trials

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## Conflict of interest

None declared

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## Abstract

**Introduction.** Proton pump inhibitors (PPIs) and histamine type-2 receptor antagonists (H2RAs) are generally effective in preventing delayed bleeding and healing artificial wounds after endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). This study aimed to review the therapeutic effects of PPIs and H2RAs on damage caused by EMR and ESD.

**Materials and methods.** Thirteen articles were collected between 2002 and 2022 by searching Medlib, ScienceDirect, PubMed, International Scientific Indexing (ISI), Embase, and Scopus databases using valid keywords. The main inclusion criteria were delayed wound healing, bleeding, epigastric pain, intraoperative bleeding, and perforation. The odds ratio (OR) and 95% confidence interval (95% CI) were evaluated using a random or fixed effects model. Data analysis was performed using Stata v. 14.2.

**Results.** A total of 13 articles including 1,483 patients were analyzed. The results showed that delayed bleeding was significantly less frequent in the PPI group than in the H2RA group (OR = 0.6; 95% CI: 0.39–0.92). Subgroup analysis showed that PPI was more effective in preventing delayed bleeding than H2RA for ESD wounds (OR = 0.65; 95% CI: 0.44–1.08). There was no statistically significant difference between both groups regarding the incidence of epigastric pain, intraoperative bleeding, wound healing, and perforation after endoscopic treatments.

**Conclusions.** The meta-analysis results reveal that PPI is more effective than H2RA in preventing delayed bleeding after endoscopic treatment, particularly in patients treated with ESD. However, there was no significant difference between PPI and H2RA in terms of intraoperative bleeding, epigastric pain, wound healing, and perforation from endoscopic therapy.

**Key words:** endoscopic mucosal resection, endoscopic submucosal dissection, proton pump inhibitor, histamine H2 receptor antagonist

## Introduction

Endoscopic mucosal resection (EMR) is a common treatment for gastric and colonic neoplasms, such as early gastric cancer and adenomas.<sup>1</sup> The procedure involves injecting physiological saline into the submucosa to remove the lesion using a snare device with electrocautery.<sup>2</sup> However, EMR is less effective for block resection of lesions larger than 2 cm.<sup>3</sup>

In late 1990s, endoscopic submucosal dissection (ESD) emerged as a procedure enabling the resection of lesions larger than 2 cm. The procedure involves 3 main steps: 1) injecting fluid into the submucosa to elevate the lesion, 2) cutting the surrounding mucosa of the lesion, and 3) dissecting the submucosa beneath the lesion.<sup>4</sup> Endoscopic submucosal dissection facilitates histological evaluations and minimizes the risk of local recurrence.<sup>5,6</sup> However, it has a higher risk of complications and causes more profound and extensive artificial ulcerations than EMR.<sup>7,8</sup> Both methods carry significant difficulties, including bleeding, perforation and aspiration pneumonitis.<sup>9,10</sup> Postoperative bleeding is the most common complication of ESD, occurring in 5–10% of cases, although this percentage varies in different studies.<sup>11</sup> Ulcer bleeding is more likely to occur after ESD than EMR due to the larger resected area, and delayed bleeding is closely linked to lesion size.<sup>12</sup>

For the management and control of ulcer bleeding, mainly 2 groups of gastric acid secretion inhibitors are administered: proton pump inhibitors (PPIs) and histamine type-2 receptor antagonists (H2RAs). The healing rate of peptic ulcers treated with PPIs is faster than that of patients treated with H2RA because of their more robust antiacid effectiveness. Studies have shown that H2RA activity is substantially quicker and less expensive than PPIs despite having a lower potency.<sup>13,14</sup> Proton pump inhibitors and H2RAs have been compared therapeutically in randomized controlled trials<sup>1,15,16</sup> to treat artificial ulcers following endoscopic treatments. Proton pump inhibitors and H2RAs neutralize pH levels and allow to avoid bleeding following ESD. In several earlier investigations, PPIs were found to be favored over H2RA.<sup>15</sup> However, PPIs, or substituted benzoimidazoles, decrease the generation of acid by blocking the parietal cell hydrogen-potassium adenosine-triphosphatase enzyme system in the gastric mucosa.<sup>16</sup>

## Objectives

We performed a systematic review and meta-analysis of randomized trials in this study to examine the therapeutic effects of PPIs and H2RAs for treating iatrogenic stomach ulcers following ESD or EMR.

## Methods

### Search strategy

The aim of this meta-analysis was to compare the effectiveness of PPIs and H2RAs in controlling bleeding and speeding up wound healing after EMR or ESD. The study was conducted by reviewing literature and electronic databases from 2000 until November 2022. Studies were selected from scientific journals and articles available in PubMed, Medlib, ScienceDirect, International Scientific Indexing (ISI), Scopus, and Embase. The search was conducted using valid keywords, such as “endoscopic mucosal resection,” “endoscopic submucosal dissection,” “PPIs,” and “histamine h2 receptor antagonists”. Keywords were standardized in MESH prior to searching. The search strategy, screening and data selection were performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

### Inclusion and exclusion criteria

The meta-analysis inclusion criteria consisted of: 1) studies on patients undergoing EMR or ESD treatments, 2) patients who were treated with PPIs and H2RA for endoscopy-induced ulcers, and 3) surveys reporting at least 1 outcome, such as post-endoscopy bleeding, and epigastric pain, and wound healing. The exclusion criteria included: 1) non-randomized and uncontrolled reviews, 2) qualitative and descriptive studies, 3) articles presented at conferences, 4) review articles, systematic reviews and meta-analyses, as well as 5) articles published in language other than English.

### Study selection

Using Endnote X8 (Clarivate Plc, London, UK), 2 researchers examined article titles and abstracts and then screened them according to the inclusion and exclusion criteria (Fig. 1). Papers meeting the criteria were further evaluated by reading their full text. In cases of disagreement between the 2 researchers, a 3<sup>rd</sup> expert made the final judgement. Quality assessment was conducted using the methods recommended in the Cochrane Handbook for Systematic Reviews of Interventions (Fig. 2,3).<sup>17</sup> The articles' bias risk was evaluated by 2 reviewers using 7 criteria: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). Each criterion was classified as “low risk,” “high risk” or “unclear risk.”

### Data extraction and analysis

All articles were evaluated for their homogeneity. In case of significant heterogeneity, subgroup analysis and

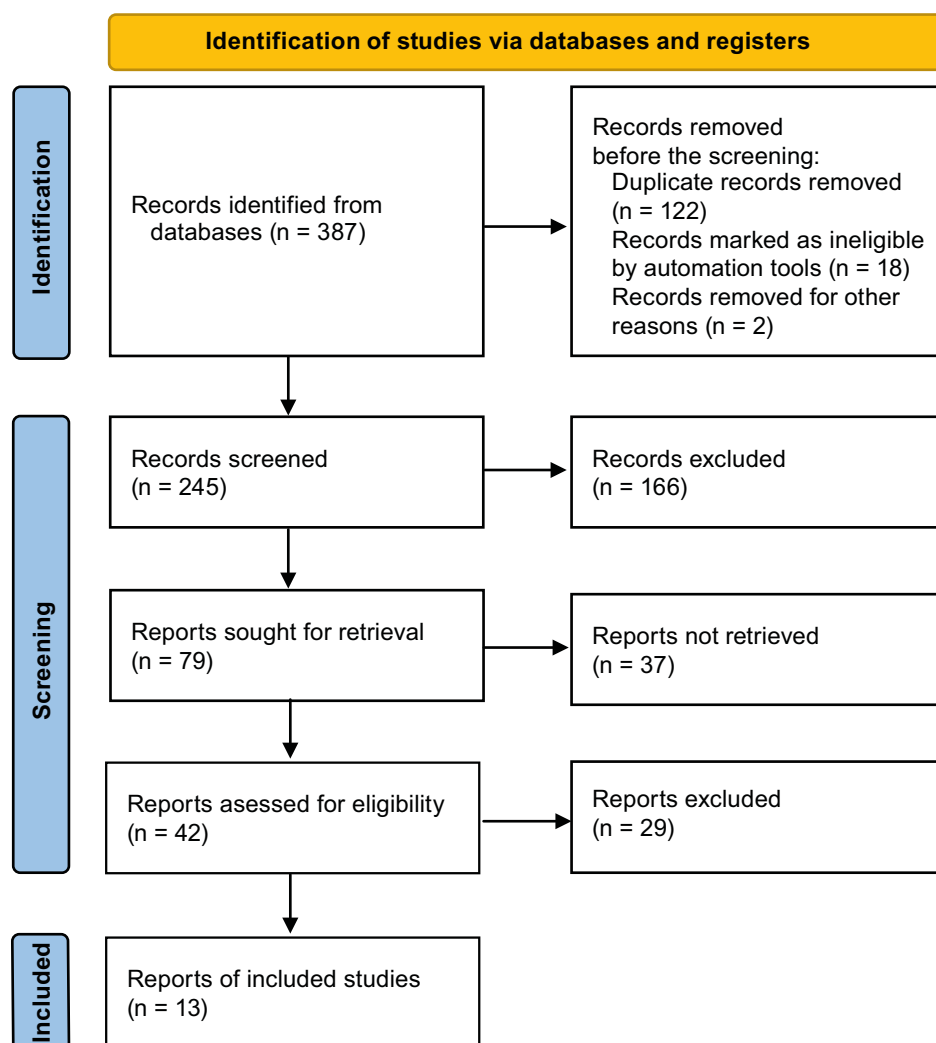


Fig. 1. Study flowchart

meta-regression were performed to examine heterogeneity. The selected papers were thoroughly reviewed, and their information was entered into a form designed and prepared for data extraction. The data was then transferred from Excel 2019 (Microsoft Corp., Redmond, USA), Review Manager v. 5.3 (RevMan 5.3; Cochrane Collaboration, London, UK) and Stata v. 14 software (StataCorp LLC, College Station, USA). The data collected included the names of the authors, year of publication, place of research, number of patients, average age and gender of participants, endoscopic treatment, type and dosage of medication, duration of the drug and follow-up, *Helicobacter pylori*-infection percentage (%), and size and location of the lesion. The main complications observed included delayed bleeding after endoscopy, epigastric pain, perforation, and change in wound size 28 days after endoscopy.

## Statistical analyses

The studies were classified according to the number of samples, mean (M) and standard deviation (SD). Each study was evaluated based on its variance. To investigate heterogeneity, we tested the Q test and  $I^2$  index for

significance at the error level of less than 5% for  $\alpha$ . If the results of the studies were heterogeneous, we analyzed them using meta-analysis (fixed- and random-effects model). Subgroup analyses were performed to consider the duration of drug use (4 and 8 weeks), the type of PPI (omeprazole and rabeprazole), the kind of endoscopy (EMR and ESD), and the use of PPI and H2RA alone or in combination with cytoprotective agents. Publication bias in the included studies of the meta-analysis was assessed using the Beggs and Egger plot. Data analysis was performed using Stata v. 14.

## Results

After removing duplicate and unrelated articles, 79 studies were reviewed. The process of selecting the analyses is shown in Fig. 3. Overall, 13 articles were included in the study. Among these articles, 10 were published as full texts and 3 trials as abstracts (with sufficient information) between 2002 and 2021 (Table 1).<sup>1,15,16,18–27</sup> Seven studies were conducted in Japan and 6 studies in South Korea. The study included 1,483 participants from the southern region, with 793 subjects in the PPI group

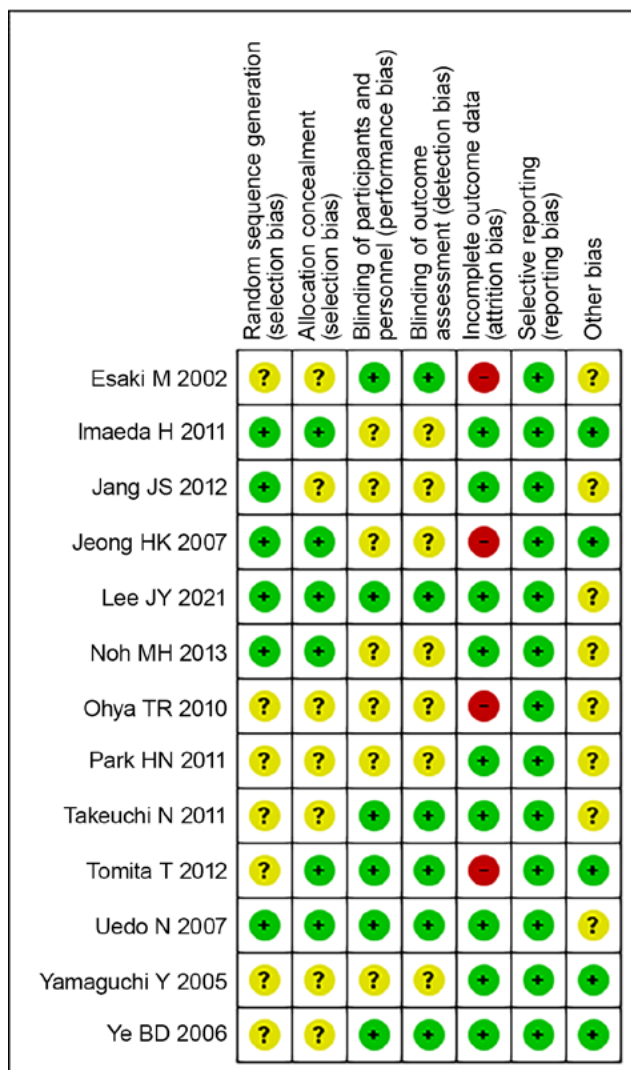


Fig. 2. Risk of bias summary across studies

and 790 in the H2RA group. The average age of the participants was 66.09 years in the PPI group and 66.6 years in the H2RA group. Additionally, the prevalence of *H. pylori* was 0.73% and 0.71% in the PPI and H2RA groups, respectively. The average pH was 6.2 in the PPI group and 5.3 in the H2RA group.

The duration of drug use was 28 days in 8 articles and 56 days in 5 papers. Proton pump inhibitors and H2RA were examined alone in 10 studies and in combination with cytoprotective agents in 3 articles. The funnel plots show the publication bias symmetrically, the *p*-value was 0.484, showing no possibility of publication bias across studies based on the delayed bleeding data (Fig. 4). Similarly, no possibility of publication bias across studies was shown based on the wound healing data, with a *p*-value of 0.348 (Fig. 5).

## Delayed bleeding

In 11 trials involving 1,407 patients (755 receiving PPI and 752 receiving H2RA), the effect of PPI was compared to that of H2RA on delayed bleeding after endoscopic treatments. Based on the fixed-effects model, in comparison to H2RA, PPI treatment was significantly effective in preventing bleeding after gastric endoscopic treatment (odds ratio (OR) = 0.6; 95% confidence interval (95% CI): 0.4–0.90; *p* = 0.01; Fig. 6). For sensitivity analysis, excluding the 3 trials that used cytoprotective agents, did not change the results (OR = 0.66; 95% CI: 0.43–1.02; *p* = 0.04; Table 2). No significant difference was observed between PPI and H2RA in the delayed bleeding prevention subsequently endoscopic treatments with omeprazole (OR = 0.99; 95% CI: 0.41–2.41; *p* = 0.98) and rabeprazole (OR = 0.53; 95% CI: 0.21–0.23; *p* = 0.13). In the subgroup analysis with 4-week medication, PPI was pointedly more operative than H2RA in preventing delayed bleeding after endoscopic treatment (OR = 12.9; 95% CI: 5.56–30.26; *p* = 0.000). The same result was found in the subgroup that received 8-week drugs (OR = 0.53; 95% CI: 0.31–0.91; *p* = 0.02). Both PPI and H2RA were tested separately (OR = 0.66; 95% CI: 0.43–1.02; *p* = 0.04) and in combination with cytoprotective agents (OR = 0.31; 95% CI: 0.13–0.95; *p* = 0.03). The PPI was more efficient than H2RA in preventing bleeding. In the subgroup undergoing EMR, there was no significant difference between PPI and H2RA in preventing bleeding (OR = 0.94; 95% CI: 0.73–1.32; *p* = 0.56), while in the EDS subgroup, PPI was more effective than H2RA in preventing bleeding after endoscopy (OR = 0.65; 95% CI: 0.44–1.08; *p* = 0.03).

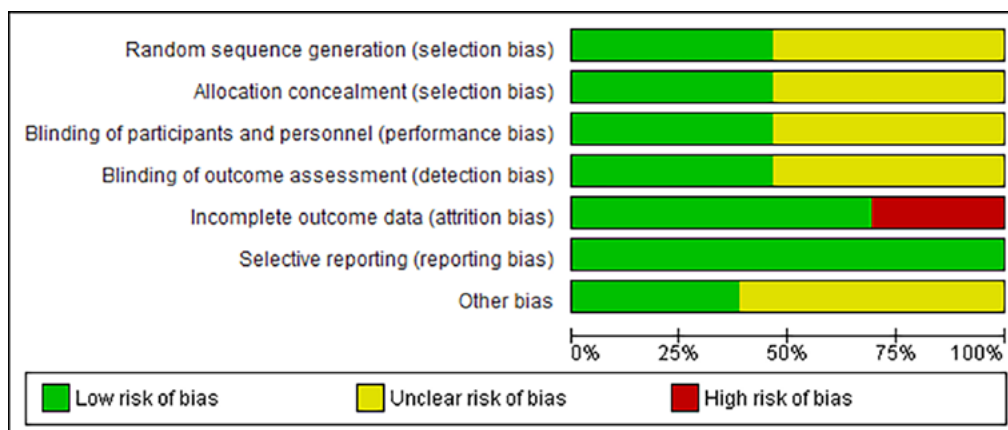


Fig. 3. Details of quality assessment for each included study are represented for each risk of bias item: low risk of bias (green), unclear risk of bias (yellow) and high risk of bias (red)

**Table 1.** Study characteristics

Authors and reference	Country	Year	Study design	Lesion size [mm]	Percentage of tumor location [upper/middle/lower]	Hp positive – city [%]	Percentage of gender [M/F]	Age [years]	Dosage [mg/day]	Treatment (n)	Follow-up time [days]	Medication duration [days]	Endoscopic therapy	Number of participants
Ye et al. <sup>1</sup>	South Korea	2006	prospective randomized controlled trial	11 11	2/32/66 2/27/71	61 56	68/32 59/41	61 59	20 40	omeprazole (41) famotidine (41)	28	28	EMR + ESD	82
Esaki et al. <sup>15</sup>	Japan	2002	prospective randomized controlled trial	18 20	0/12/88 0/37/63	88 63	88/12 63/37	62 70	20 40	omeprazole (8) famotidine (8)	28	28	EMR	16
Uedo et al. <sup>16</sup>	Japan	2007	prospective randomized controlled trial	41 1	0/47/53 0/38/62	81 86	78/22 79/21	68 66	20 800	rabeprazole (73) cimetidine (70)	56	56	ESD	143
Tomita et al. <sup>18</sup>	Japan	2012	prospective randomized controlled trial	43.8 40.3	12/32/33 16/33/30	–	76/24 74/26	70.4 70.6	20 40	omeprazole (77) famotidine (79)	56	56	ESD	156
Ohya et al. <sup>19</sup>	Japan	2010	prospective randomized trial	35 33	12/59/29 4/53/43	77 79	74/26 72/28	65 65	10 20	rabeprazole (31) lafutidine (29)	28	28	ESD	60
Imaeda et al. <sup>20</sup>	Japan	2011	prospective randomized trial	37.7 36.3	0/42/20 0/36/25	61 62	76/24 85/15	68.4 67.6	30 150	lansoprazole (62) roxatidine (61)	56	56	ESD	123
Jeong et al. <sup>21</sup>	South Korea	2007	prospective randomized trial	18 19	0/31/69 0/28/72	62 64	65/35 67/33	63 64	40 40	pantoprazole (85) famotidine (79)	90	56	ESD	164
Lee and Jang <sup>22</sup>	South Korea	2021	prospective randomized controlled trial	28 30	5/4/42 4/5/43	–	60/40 75/25	62.4 70.6	20+100 400+100	rabeprazole + rebamipide (52) cimetidine + rebamipide (52)	28	28	ESD	104
Noh et al. <sup>23</sup>	South Korea	2013	prospective randomized controlled trial	–	–	–	–	–	–	PPI + cytoprotective (92) H2RA + cytoprotective (98)	28	28	ESD	190
Jang et al. <sup>24</sup>	South Korea	2012	prospective randomized controlled trial	–	–	–	–	–	–	PPI + cytoprotective (110) H2RA + cytoprotective (111)	28	28	ESD	121
Yamaguchi et al. <sup>25</sup>	Japan	2005	prospective randomized trial	28 22	3/62/35 0/71/29	83 81	69/31 82/18	72 73	20 40	omeprazole (29) famotidine (28)	60	56	EMR + ESD	57
Takeuchi et al. <sup>26</sup>	Japan	2011	prospective randomized trial	–	14/10/6 12/9/9	76 80	66/34 70/30	68.7 67.4	10 150	rabeprazole (30) roxatidine (30)	56	28	ESD	60
Park et al. <sup>27</sup>	South Korea	2011	prospective randomized controlled trial	–	–	–	–	–	–	PPI (103) H2RA (104)	28	28	ESD	207

PPI – proton pump inhibitors; H2RA – histamine-2-receptor antagonists; EMR – endoscopic mucosal resection; ESD – endoscopic submucosal dissection.

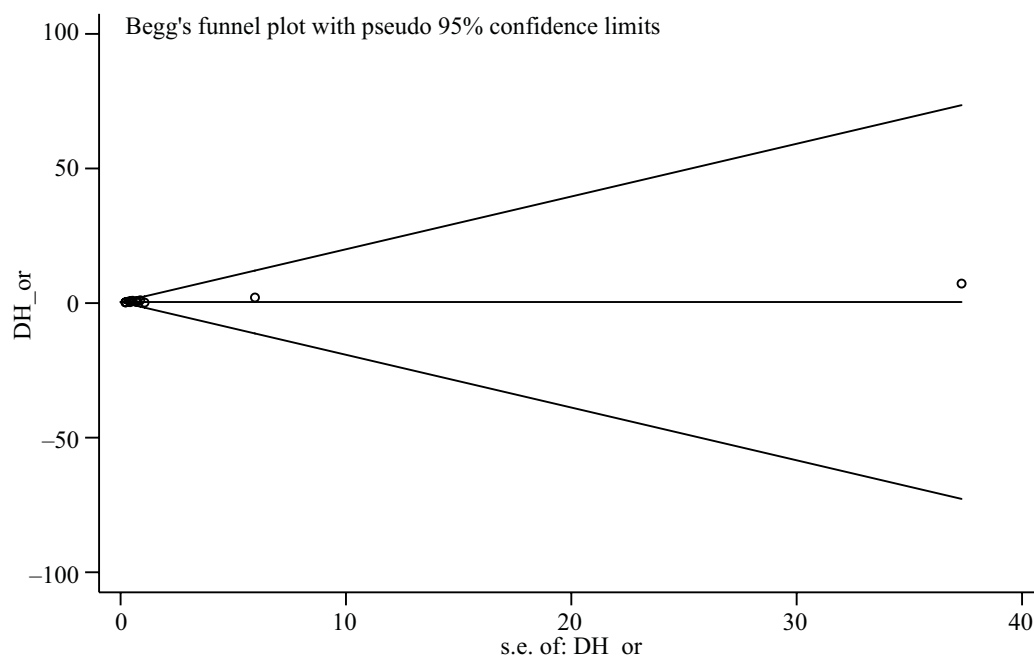


Fig. 4. Publication bias diagram. The circles show the weight of the studies based on the delayed bleeding data ( $p = 0.484$ )

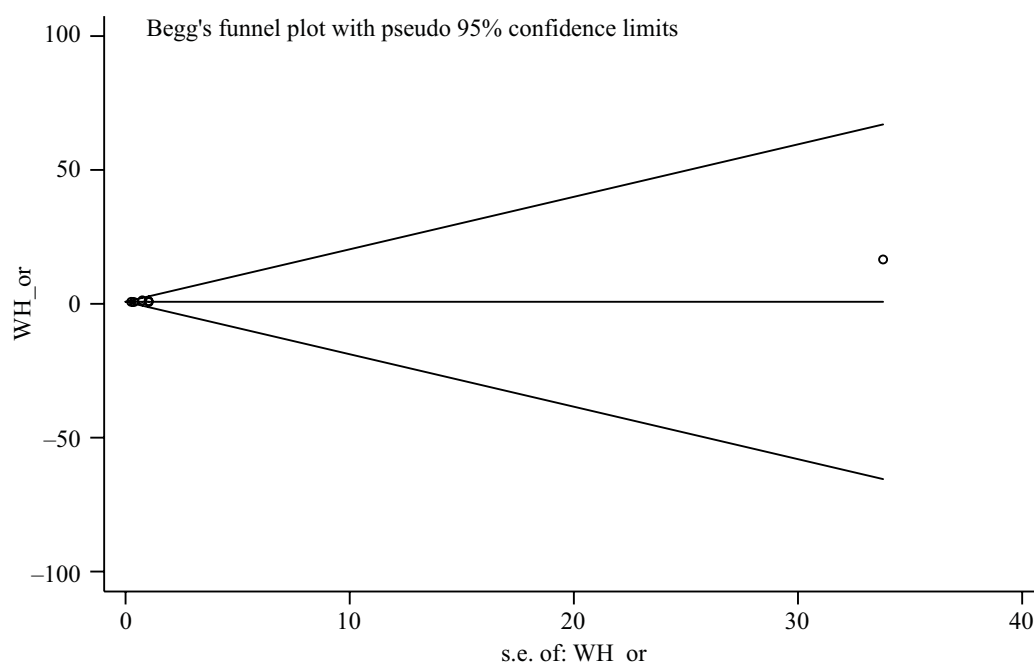


Fig. 5. Publication bias diagram. The circles show the weight of the studies based on the wound healing data ( $p = 0.348$ )

### Intraoperative bleeding

In 3 trials, intraoperative bleeding was reported in 287 patients receiving PPI and in 281 patients receiving H2RA. No significant difference was detected in intraoperative bleeding in the 2 patient groups ( $OR = 1.55$ ; 95% CI: 0.93–2.61;  $p = 0.094$ ).

### Wound healing

Wound healing caused by EMR or ESD was investigated in 6 trials. These studies included 668 patients – 335 in the PPI group and 333 in the H2RA group. Based on the random-effects model, there was no significant

difference between PPI and H2RA in wound healing after endoscopy ( $OR = 0.92$ ; 95% CI: 0.6–1.4;  $p = 0.7$ ; Fig. 7). The sensitivity analysis of all 6 trials, excluding 1 trial that used cytoprotective agents, did not change the results. In addition, no significant difference between PPI and H2RA in wound healing was found between 4-week ( $OR = 2.1$ ; 95% CI: 0.4–11.02;  $p = 0.37$ ) and 8-week ( $OR = 0.74$ ; 95% CI: 1.21–0.45;  $p = 0.23$ ) medication.

### Epigastric pain

Three trials reported epigastric pain after endoscopy in 122 patients receiving PPI and 119 patients receiving H2RA. The results of the trials were combined, and



**Table 2.** Odds ratio for therapeutic endoscopic outcomes

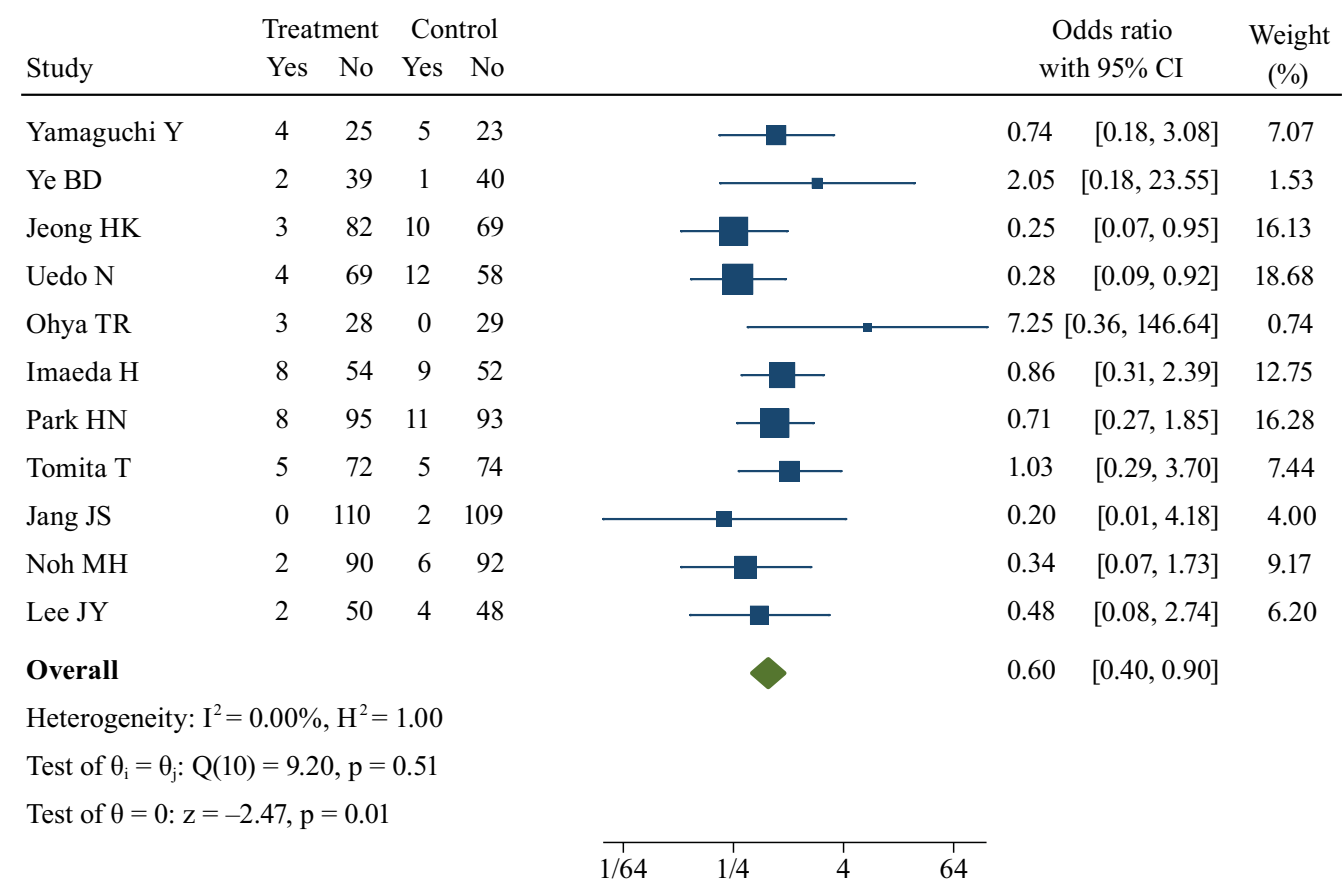
p-value	Pooled OR (95% CI)	Subgroup	Outcome
0.01	0.6 (0.39–0.92)		delayed bleeding
0.98	0.99 (0.41–2.41)	omeprazole	–
0.13	0.53 (0.23–1.21)	rabeprazole	–
0.00	12.9 (5.56–30.26)	4 weeks	–
0.02	0.53 (0.31–0.91)	8 weeks	–
0.04	0.66 (0.43–1.02)	alone	–
0.03	0.31 (0.13–0.95)	combined	–
0.56	0.94 (0.73–1.32)	EMR	–
0.03	0.65 (0.44–1.08)	ESD	–
0.09	1.55 (0.93–2.61)	–	surgery bleeding
0.2	0.64 (0.30–1.38)	–	epigastric pain
0.8	1.05 (0.71–1.57)	–	wound healing
0.37	2.1 (0.4–11.02)	4 weeks	–
0.23	0.74 (0.45–1.21)	8 weeks	–
0.5	1.5 (0.43–5.26)	–	perforation

OR – odds ratio; 95% CI – 95% confidence interval; PPI – proton pump inhibitors; H2RA – histamine-2-receptor antagonists; EMR – endoscopic mucosal resection; ESD – endoscopic submucosal dissection.

a consolidated OR = 0.64 was obtained. Also, there was no statistical difference between PPI compared to H2RA for treating epigastric pain after EMR or ESD (OR = 0.64; 95% CI: 0.30–1.38;  $p = 0.25$ ).

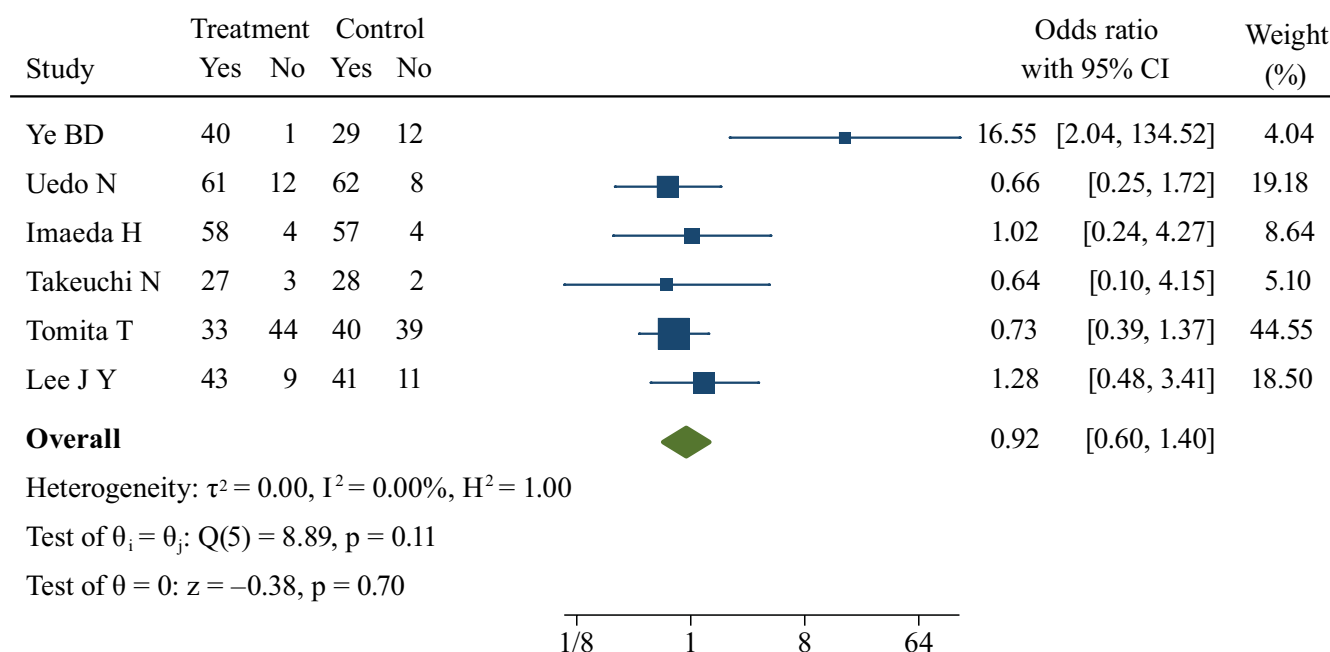
## Perforation

Four trials involving 119 patients receiving PPI and 290 patients receiving H2RA reported endoscopy-related perforation. The combined results of the trials indicated a consolidated OR = 0.52. Additionally, studies showed no significant difference between PPI and H2RA in treating epigastric pain after endoscopy (OR = 1.5; 95% CI: 0.43–5.26;  $p = 0.52$ ). The mean change in wound size 28 days after EMR or ESD was 20.3 mm in the PPI group and 20.7 mm in the H2RA group, indicating no significant difference between the 2 groups ( $p = 0.86$ ). Table 3 shows the frequency of intraoperative bleeding, delayed bleeding, epigastric pain, perforation, and wound healing rate in both the PPI and H2RA groups.



## Fixed-effects Mantel–Haenszel model

**Fig. 6.** The odds ratio (OR) for delayed bleeding between PPI and H2RA groups ( $p = 0.018$ ). Each square shows the effect estimate of individual studies with their 95% confidence interval (95% CI). The size of the courts is proportional to the weight of each study in the meta-analysis. This plot shows studies in the order of publication date and first author's name (based on a fixed-effects model)



### Random-effects REML model

**Fig. 7.** The odds ratio (OR) for wound healing between PPI and H2RA groups ( $p = 0.7$ ). Each square shows the effect estimate of individual studies with their 95% confidence interval (95% CI). The size of the courts is proportional to the weight of each study in the meta-analysis. This plot shows studies in the order of publication date and first author's name (based on a random-effects model)

**Table 3.** The average frequency of intraoperative bleeding, delayed bleeding, epigastric pain, perforation, and wound healing rate in PPI and H2RA groups

Frequency (%)		Outcome
H2RA	PPI	Medication
21	25	surgery bleeding
8.7	6.3	delayed bleeding
29	17	epigastric pain
78	81	wound healing
13	18	perforation

PPI – proton pump inhibitors; H2RA – histamine-2-receptor antagonists.

## Discussion

Endoscopic therapy is considered for managing primary gastric malignancies.<sup>18</sup> An artificial pattern of acute gastric ulcer is created through EMR or ESD.<sup>28</sup> Acid-suppressive agents are prescribed to prevent bleeding and induce rapid wound healing caused by EMR or ESD. Since the blood coagulation system is sensitive to pH changes in the stomach, acid-blocking drugs can help stabilize blood clots by maintaining a neutral pH in the stomach, and inhibit frequent bleeding and rapid wound healing.<sup>29,30</sup>

Proton pump inhibitors and H2RA are both acid-inhibiting agents. Even though PPIs are more potent inhibitors of gastric acid secretion than H2RA, it has been reported that H2RAs act significantly faster than PPIs.<sup>1,13</sup> Several studies have compared PPIs with H2RAs in preventing

delayed bleeding and wound healing caused by EMR and ESD, and the results were contradictory.<sup>1,15,16,19,20,31</sup> Some studies have reported that treatment with PPIs is superior to that of H2RAs,<sup>1,16</sup> while other investigations have shown no difference between the 2 treatments.

The aim of this study was to elaborate and combine the findings of previous studies and meta-analyses about evaluating the effect of PPI compared to H2RA on bleeding management and wound healing after EMR or ESD. This meta-analysis shows that PPI prevents delayed bleeding in patients after endoscopic treatment better than H2RA, particularly in patients receiving ESD treatment. However, PPI and H2RA were not significantly different from endoscopic therapy in intraoperative bleeding, epigastric pain, wound healing, and perforation. These findings conform with previous meta-analyses in this field.<sup>32,33</sup> Stomach pH affects blood coagulation and the accumulation of platelets at the bleeding site. Additionally, pepsin, which digests blood clots at the wound opening, is active at a pH of less than 5. In laboratory conditions, platelet function is severely impaired at low pH.<sup>34</sup> Therefore, reducing stomach acidity to neutral stabilizes the clotting mechanism and prevents bleeding.<sup>35</sup> Proton pump inhibitors are more effective in raising intragastric pH than H2RAs. It has been reported that intragastric pH was significantly higher in patients who had taken PPI the day before ESD than those who had taken H2RA.<sup>16</sup> This meta-analysis suggests that PPI is more effective than H2RA in preventing delayed bleeding in patients after endoscopic treatment, particularly in those receiving ESD treatment.



In the subgroup analysis of endoscopic treatment, PPI was more effective than H2RA in preventing bleeding only in patients treated with ESD and not those treated with EMR. The success rate of block removal is increased using ESD, a novel technique built on EMR, which enables the removal of larger lesions.<sup>35</sup> However, it causes a significant amount of mucosal detachment, which increases the risk of harm to submucous tissues and the superficial layer of the muscularis propria surrounding blood vessels. As a result, ESD produces an artificial wound that is wider and deeper than EMR.<sup>16</sup> Wound bleeding is more common in ESD than in EMR due to the large resected area because delayed bleeding is highly connected to the lesion size.<sup>18</sup> The findings of this study showed that PPI had a better effect on large gastric ulcers caused by ESD, while it had an equivalent impact on H2RA on small ulcers caused by EMR. This finding is consistent with the previous meta-analysis.<sup>32</sup>

The PPI subgroup analysis showed no discernible difference between the groups that received omeprazole and those that received rabeprazole. According to a meta-analysis by Zhang et al., the type of PPI used to manage upper gastrointestinal bleeding following endoscopy has little to no impact,<sup>33</sup> which is consistent with the results obtained in our study. It has also been highlighted that there is no significant difference between different PPI doses regarding wound healing and bleeding control after ESD.<sup>36</sup> Furthermore, we discovered that PPI prevented bleeding better than H2RA in 4- and 8-week treatments. It has already been shown that the duration of PPI treatment does not affect wound healing and bleeding.<sup>30</sup>

Studies have reported that PPIs are more effective than H2RA in preventing bleeding.<sup>32,37</sup> It has also been suggested that the combined treatment of PPI and cytoprotective agents, including rebamipide, may be effective in iatrogenic wound healing.<sup>32</sup> Prospective randomized trials showed that combined drugs could facilitate the speed of wound healing and improve treatment outcomes.<sup>38–40</sup> On the other hand, some trials have indicated limited or no effect of combined medication on bleeding and wound healing.<sup>22–24</sup> Our study showed that using PPI alone or with cytoprotective agents is more effective in preventing bleeding after ESD than H2RA.

Proton pump inhibitors or H2RAs promote fast healing of artificial gastric ulcers after EMR or ESD. Since PPIs are more potent than H2RAs in increasing intragastric pH, it can be hypothesized that PPIs promote faster wound healing and prevent bleeding episodes more effectively than H2RAs after EMR or ESD.<sup>35</sup> However, many studies have found no difference between PPI and H2RA in wound healing.<sup>15,16,25,32,35</sup> Our meta-analysis also did not show a significant difference between PPI and H2RA in the healing of gastric ulcers after EMR and ESD.

No severe side effects were reported in the included studies. It is crucial to evaluate both acute and chronic side effects of PPIs and H2RAs, as treatment duration may range

from 3 days to several weeks. The findings indicated that the adverse effects of these 2 medication classes are minor and transient.<sup>33</sup> The study suggests that the adverse effects of PPIs and H2RAs are minor and transient, with a frequency of 1–3%.<sup>41,42</sup> These medications frequently cause nausea, vomiting, headaches, constipation, flatulence, diarrhea, stomach discomfort, and dizziness.<sup>43</sup> These are just a few of the common side effects. The most severe side effect following ESD or EMR, which was not statistically different in the 2 groups, was epigastric discomfort in the trials examined in this meta-analysis. This conclusion aligns with those of earlier studies.<sup>16,32</sup> According to studies by Esaki et al. and Uedo et al., lesion size and tumor site are associated with bleeding and wound healing.<sup>15,16</sup> However, it required much effort to categorize patients in the current meta-analysis based on these variables. Although *H. pylori* infection is a known contributor to the pathophysiology,<sup>16,44,45</sup> it has no influence on wound healing or bleeding following ESD.

## Limitations


This meta-analysis has some limitations. First, there was no information on delayed bleeding, epigastric pain or wound healing in any of the included investigations. In addition, there may have been slight differences in assessing delayed bleeding and the wound healing process, although each study clearly defined outcomes. Second, different drugs were used in the studies included. Other types of PPI and H2RA may have introduced some bias. Third, all included trials were from Japan and South Korea, and no relevant data were published from Western countries. Additionally, it is important to consider the potential for publication bias, as the number of papers included and the variations in sample size may have an influence on the results.


## Conclusions

According to this meta-analysis, PPIs are more effective than H2RAs in preventing delayed bleeding in patients undergoing endoscopic therapy, particularly those receiving ESD. The effects of endoscopic treatment on intraoperative bleeding, epigastric discomfort, wound healing, and perforation did not substantially differ between PPI and H2RA. However, more reliable evidence for PPI or H2RA treatment using various administration techniques in other regions worldwide must be obtained, particularly through large-scale randomized controlled studies.


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