META-ANALYSIS

Proton pump inhibitors therapy *vs* H₂ receptor antagonists therapy for upper gastrointestinal bleeding after endoscopy: A meta-analysis

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Abstract

AIM: To compare the therapeutic effects of proton pump inhibitors *vs* H₂ receptor antagonists for upper gastrointestinal bleeding in patients after successful endoscopy.

METHODS: We searched the Cochrane library, MEDLINE, EMBASE and PubMed for randomized controlled trials until July 2014 for this study. The risk of bias was evaluated by the Cochrane Collaboration's tool and all of the studies had acceptable quality. The main outcomes included mortality, re-bleeding, received surgery rate, blood transfusion units and hospital stay time. These outcomes were estimated using odds ratios (OR) and mean difference with 95% confidence interval (CI). RevMan 5.3.3 software and Stata 12.0 software were used for data analyses.

RESULTS: Ten randomized controlled trials involving 1283 patients were included in this review; 678 subjects were in the proton pump inhibitors (PPI) group and the remaining 605 subjects were in the H₂ receptor antagonists (H₂RA) group. The meta-analysis results revealed that after successful endoscopic therapy, compared with H₂RA, PPI therapy had statistically significantly decreased the recurrent bleeding rate (OR = 0.36; 95%CI: 0.25-0.51) and receiving surgery rate (OR = 0.29; 95%CI: 0.09-0.96). There were no statistically significant differences in mortality (OR = 0.46; 95%CI: 0.17-1.23). However, significant heterogeneity was present in both the numbers of patients requiring blood transfusion after treatment [weighted mean difference (WMD), -0.70 unit; 95%CI: -1.64 - 0.25] and the time that patients remained hospitalized [WMD, -0.77 d; 95%CI: -1.87 - 0.34]. The Begg's test (*P* = 0.283) and Egger's test (*P* = 0.339) demonstrated that there was no publication bias in our meta-analysis.

CONCLUSION: In patients with upper gastrointestinal bleeding after successful endoscopic therapy, compared with H₂RA, PPI may be a more effective therapy.

Core tip: Recently, the administration of proton pump inhibitors (PPI) or H$_2$ receptor antagonists (H$_2$RA) have been used commonly for upper gastrointestinal bleeding patients after successful endoscopic therapy; however, which drug class is more effective, remains controversial. In this meta-analysis, we concluded that in patients with upper gastrointestinal bleeding after successful endoscopic therapy, compared with H$_2$RA, PPI may be a more effective therapy.

INTRODUCTION

Gastrointestinal (GI) bleeding is a common cause of hospitalization, resulting in approximately 400000 hospital admissions annually, with a mortality rate of 5%-10%[1]. Re-bleeding has been described as the most important factor that affects patient prognosis; therefore, the re-bleeding rate is associated with mortality[2]. Appropriate endoscopic therapy of patients with non-variceal upper gastrointestinal bleeding improves outcomes, including re-bleeding rates, mortality, surgery, blood transfusions and hospitalization time[3,4]. Moreover, *Helicobacter pylori* (*H. pylori*) infection and nonsteroidal anti-inflammatory medication (NSAID) use are believed to be the main causes of non-variceal upper gastrointestinal bleeding (UGIB)[5,6]. Consequently, many factors may affect results of studies that examine UGIB.

Recently, the administration of proton pump inhibitors (PPI) or H$_2$ receptor antagonists (H$_2$RA) has been used commonly for upper gastrointestinal bleeding patients after successful endoscopic therapy[7,8]; however, the two drugs possess different pharmacological acid-suppressing activities. PPIs are substituted benzimidazoles that inhibit the parietal cell hydrogen-potassium adenosine-triphosphatase enzyme system in the gastric mucosa, reducing acid output; whereas H$_2$RAs decrease acid secretion by interfering with the H$_2$ receptor[9]. PPIs decrease hydrogen ion concentration by 95%-99% in humans at doses of 30-40 mg/d; however, H$_2$RAs cause less acid inhibition than PPIs[10].

Several valuable randomized controlled trials (RCTs)

have compared the therapeutic effect of PPIs and H$_2$RAs in upper gastrointestinal bleeding patients after successful endoscopic therapy. Additionally, the meta-analysis of Yang *et al*[11] only evaluated the re-bleeding rate in two groups to perform a one-sided comparison of the curative effect of two drugs. Therefore, in this study, we expanded the sample size to analyze the effect of PPI therapy *vs* H$_2$RAs therapy from these RCTs, with data pertaining to recurrent bleeding rate, mortality, receive surgery rate, blood transfusion units and hospitalization time.

MATERIALS AND METHODS

Data selection

The following keywords, proton pump inhibitors, PPI, H$_2$ receptor antagonists, H$_2$RA, endoscopic, bleeding, randomized controlled trial and clinical trial, were used as search terms in the Cochrane library, MEDLINE, EMBASE and PubMed until July 2014.

Inclusion criteria

The inclusion criteria for this study were: (1) all patients in the experimental group were diagnosed with any type of upper gastrointestinal bleeding after successful endoscopic therapy; (2) comparison therapies of proton pump inhibitors or H$_2$ receptor antagonists in similar baseline level patients; (3) the end-points included recurrent bleeding rate; (4) randomization, controls, and measurable outcomes were reported; and (5) the articles were written in English.

Data extraction

The articles were extracted independently by two investigators and any disagreements were resolved by discussion or by asking the third investigator. The first author's name, publication year, sample size, participants' age, participants' gender, smoking (%), alcohol abuse (%), positive *H. pylori* infection (%), NSAID user (%), drug type, intervention measure and outcome assessment time were extracted. The main outcomes included were: (1) mortality (*n*); (2) re-bleeding (*n*); (3) received surgery (*n*); (4) blood transfused (unit/500 mL); and (5) hospitalization stay time (d).

Study quality assessment

We used the Cochrane Collaboration's tool[12] to evaluate the quality of the articles. The following seven items of risk of bias in the tool were assessed: 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), selective reporting (reporting bias) and Other bias, all studies were classified as low risk, high risk and unclear risk. The assessment was performed
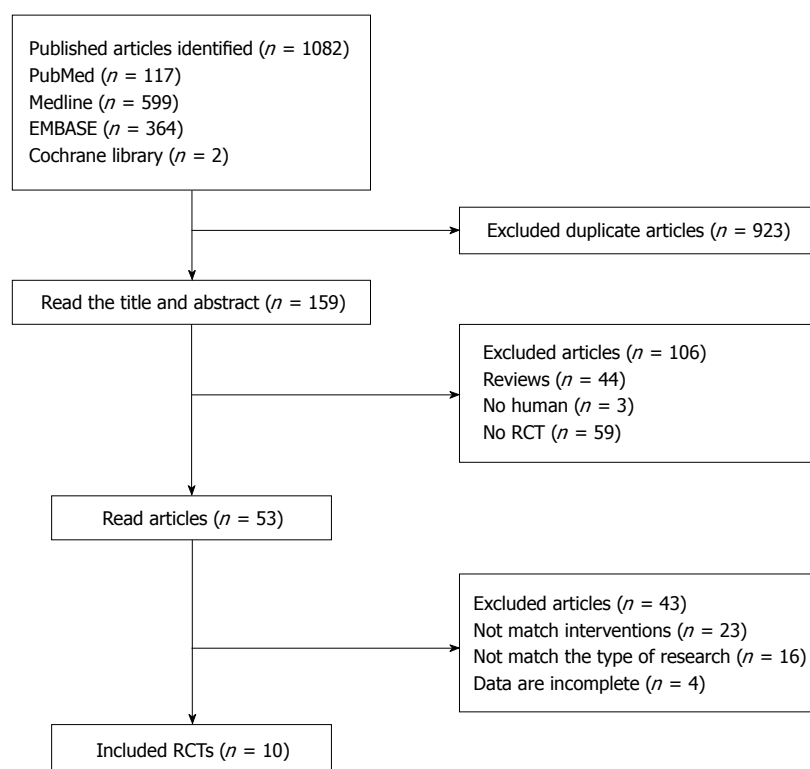
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┌─────────────────────────────────────────┐
│ Published articles identified (n = 1082)  │
│ PubMed (n = 117)                          │
│ Medline (n = 599)                         │
│ EMBASE (n = 364)                          │
│ Cochrane library (n = 2)                  │
└─────────────────────────────────────────┘
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                  │──────────────────────────→ ┌──────────────────────────────────┐
                  │                             │ Excluded duplicate articles (n = 923) │
                  ↓                             └──────────────────────────────────┘
┌─────────────────────────────────────────┐
│ Read the title and abstract (n = 159)     │
└─────────────────────────────────────────┘
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                  │──────────────────────────→ ┌──────────────────────────────────┐
                  │                             │ Excluded articles (n = 106)        │
                  │                             │ Reviews (n = 44)                   │
                  │                             │ No human (n = 3)                   │
                  ↓                             │ No RCT (n = 59)                    │
┌─────────────────────────────────────────┐   └──────────────────────────────────┘
│ Read articles (n = 53)                    │
└─────────────────────────────────────────┘
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                  │                             │ Excluded articles (n = 43)                 │
                  │                             │ Not match interventions (n = 23)           │
                  │                             │ Not match the type of research (n = 16)    │
                  ↓                             │ Data are incomplete (n = 4)                │
┌─────────────────────────────────────────┐   └──────────────────────────────────────────┘
│ Included RCTs (n = 10)                    │
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Figure 1 Flow chart of study selection. RCTs: Randomized controlled trials.

independently by two investigators; disagreements were be resolved by discussion or by involving the third investigator.

Statistical analysis

At the end of treatment for the individual trials, the odds ratio (OR) and mean difference (MD) with their 95% confidence interval (CIs) were calculated. The OR and weighted mean difference (WMD) were used as summary estimators. A fixed-effect model weighted by the inverse variance method was used following a homogeneity test. We performed the homogeneity test using a χ^2 test on N-1 degrees of freedom. A *P* value of 0.05 was regarded as statistically significant, rejecting the assumption of homogeneity ($P < 0.05$), and the random-effect model was then performed using the inverse variance method. Publication biases were evaluated using a Funnel plot, Begg's test and Egger's test; $P \geqslant 0.05$ indicated there was no publication bias.

All statistical analyses were performed using Review Manager 5.3.3 statistical software (Cochrane Collaboration, Oxford, United Kingdom) and Stata 12.0 statistical software (Stata Co. College Station, TX, United States) for the meta-analysis.

RESULTS

Article selection

One-thousand and eighty-two publish articles were identified, and we initially excluded 923 duplicate articles. Then, after reading the title and abstract, 53

articles remained. Finally, by reading the full text of each article, 10 RCTs[13-22] were included in this meta-analysis (Figure 1). The characteristics of all included studies are shown in Table 1. This meta-analysis included 1283 patients, with 678 subjects in the PPI group and the remaining 605 subjects in the H$_2$RA group. The maximum sample size of the included studies was 200 cases[16]; the minimum was 77 cases[20]. For the study of Lin *et al*[16], which used two randomized controlled programs, the programs were divided into a and b programs as two separate studies and included in the meta analysis.

Use of PPI therapy compared with H$_2$RA therapy for recurrent bleeding rate and quality assessment

The number of recurrent bleeding subjects reported after treatment was investigated in all included studies[13-22]. According to the different routes of administration, the studies could be divided into three subgroups, intravenous followed by oral, simple intravenous and simple oral. There was not any significant heterogeneity between the included trials ($P = 0.13$, $I^2 = 35\%$) and subgroups ($P = 0.90$, $I^2 = 0\%$); therefore, we used the fixed effects model for the analysis. Seven of the studies[13,16,17,19-22], including 922 subjects, used the first intravenous and then oral administration method; the results of these studies did not statistically significantly reduce the re-bleeding rate (OR = 0.35; 95%CI: 0.24-0.52; Figure 2). However, one trial[15], which included 149 subjects, reported the re-bleeding number after simple intravenous treatment

Table 1 General condition sheet of the included studies

Ref.	Sample size	Age	Gender (M/F)	Smoking (%)	Alcohol abuse (%)	*H. pylori* infection positive (%)	NSAID user (%)	Drug type	Intervention		Outcome assessment time	The main outcomes
									PPI group	H₂RA group		
Hsu *et al*[13]	P:52	P: 63.2 ± 18.	P: 41/11	P: 32.7	P: 13.5	NA	P: 26.9	P: Pantoprazole	40 mg intravenous /12 h 3 d, followed by 40 mg/d orally	50 mg intravenous /8 h, followed by 150 mg /12 h orally	8 wk	1,2,3,4,5
	H:50	H: 64.7 ± 13.8	H: 37/13	H: 32.0	H: 8.0		H: 320	H: Ranitidine				
Ye *et al*[14]	P:41	P: 61.2 ± 9.0	P: 28/13	NA	NA	P: 61.0	NA	P: Omeprazole	20 mg/d orally	20 mg/12 h orally	28 d	1
	H:41	H: 58.5 ± 9.4	H: 24/17			H: 56.1		H: Famotidine				
Jensen *et al*[15]	P:72	P: 59.6 ± 16.1	P: 51/21	NA	NA	NA	P: 69	P: Pantoprazole	80 mg bolus and 8 mg/h infusion 3 d	50 mg bolus and 6.25 mg/h infusion 3 d	3 d, 7 d, 30 d	1
	H:77	H: 55.6 ± 16.8	H: 52/25				H: 71	H: Ranitidine				
Lin *et al*[16]	Pa:67	Pa: 67	Pa: 58/9	NA	NA	NA	Pa: 26.9	P: Omeprazole	a: 40 mg intravenous /12 h 3 d, followed by 20 mg/d orally	400 mg intravenous /12 h 3 d, followed by 400 mg/12 h orally	14 d	1,2,3,4,5
	Pb:66	Pb: 71	Pb: 57/9				Pb: 24.2	H: Cimetidine	b: 40 mg intravenous /6 h 3 d, followed by 20 mg/d orally			
	H:67	H: 68	H: 61/6				H: 29.9					
Jeong *et al*[17]	P:85	P: 62.9 ± 9.4	P: 52/33	NA	NA	P: 61.9	NA	P: Pantoprazole	80 mg bolus and 8 mg/h infusion d1, 40 mg intravenous /12 h d2-3, followed by 40 mg/d orally	20 mg intravenous /12 h d2, followed by 20 mg/d orally	24 h, 7 d, 14 d	1,2,3
	H:79	H: 63.5 ± 7.8	H: 53/26			H: 64.1		H: Famotidine				
Uedo *et al*[18]	P:64	P: 68.1 ± 8.5	112/33	NA	NA	11.5	11.5	P: Rabeprazole	20 mg/d orally	800 mg/d orally	8 wk	1
	H:66	H: 65.7± 7.6						H: Cimetidine				
Imaeda *et al*[19]	P:62	P: 68.4 ± 8.0	P: 47/15	P: 58.1	NA	P: 61.3	NA	P: Lansoprazole	30 mg intravenous /12 h 2 d, followed by 30 mg/d orally	75 mg intravenous /12 h 2 d, followed by 75 mg/12 h orally	8 wk	1
	H:61	H: 67.6 ± 8.5	H: 52/9	H: 49.2		H: 62.3		H: Roxatidine				
Sakurada *et al*[20]	P:40	P: 65.8 ± 2.5	P: 35/5	NA	NA	P: 77.5	P: 35.0	P: Omeprazole	20 mg intravenous /12 h 3 d, followed by 20 mg/d orally	20 mg intravenous /12 h 3 d, followed by 20 mg/d orally	6-8 wk	1,5
	H:37	H:60.2 ± 1.7	H: 31/6			H: 78.4	H: 29.7	H: Famotidine				
Tomita *et al*[21]	P:77	P: 70.4 ± 8.7	P: 59/18	NA	NA	NA	NA	P: Omeprazole	20 mg/12 h intravenous 3 d, followed by 20 mg/d orally	40 mg bolus/d	8 wk	1
	H:79	H: 70.6 ± 9.5	H: 59/20					H: Famotidine				
Lin *et al*[22]	P:50	P: 65 H: 66.5	P: 46/4	P: 34.0	P:12.0	NA	NA	P: Omeprazole	40 mg intravenous and 160 mg infusion 3 d, followed by 20 mg/12 h orally 2 m	300 mg intravenous and 1200 mg infusion 3 d, followed by 400 mg/12 h orally 2 m	3 d, 14 d	1,2,3,4,5
	H:50		H:43/7	H: 28.0	H: 12.0			H: Cimetidine				

[1]Recurrent bleeding (*n*); [2]Mortality (*n*); [3]Received surgery (*n*); [4]Blood transfused (unit); [5]Hospital stay (d). P: PPI group; H: H₂RA group; PPI: Proton pump inhibitor; H₂RA: Histamine 2 receptor antagonist; NA: Not applicable.
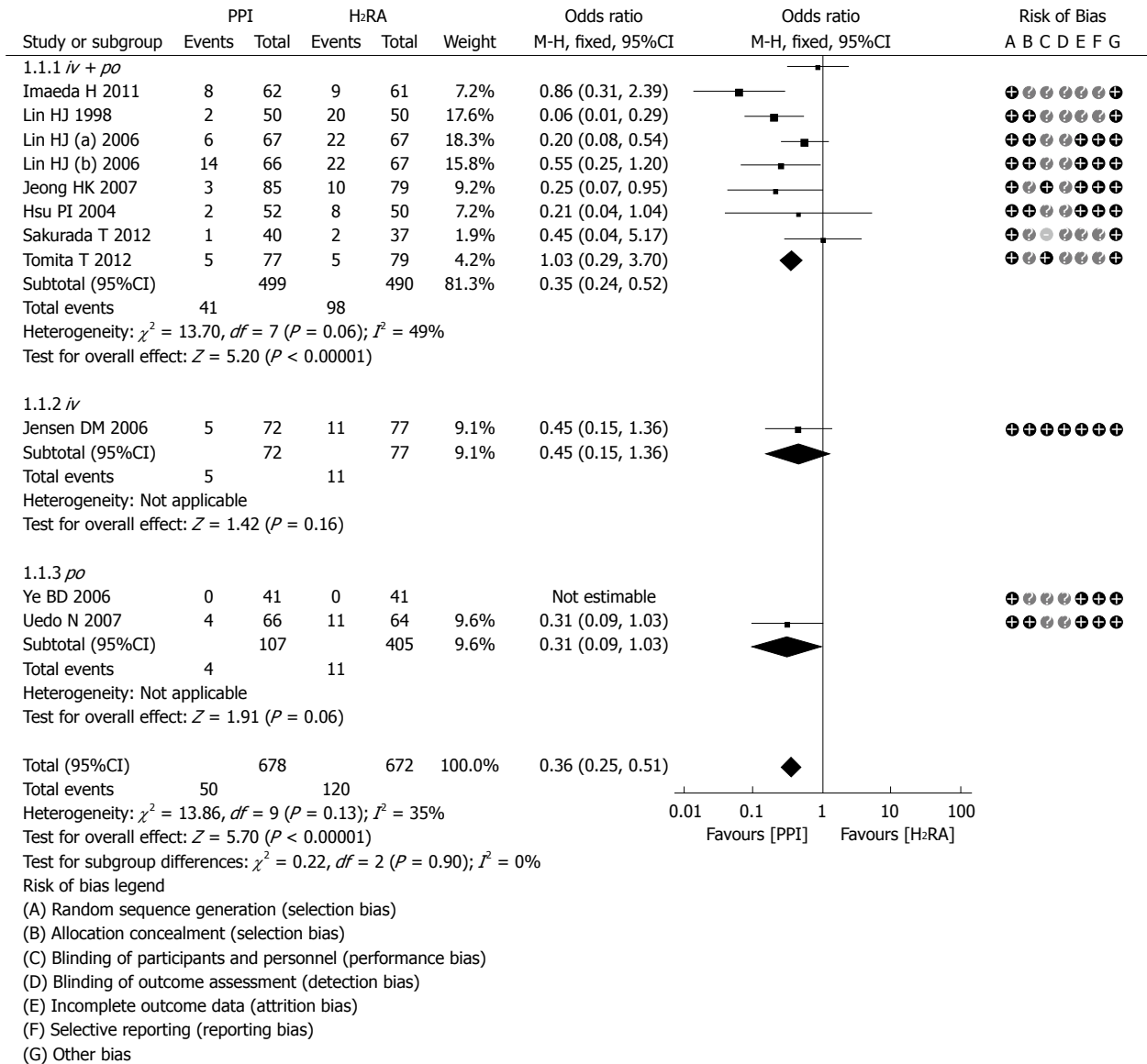
Study or subgroup	PPI Events	PPI Total	H$_2$RA Events	H$_2$RA Total	Weight	Odds ratio M-H, fixed, 95%CI	Odds ratio M-H, fixed, 95%CI	Risk of Bias A B C D E F G
1.1.1 *iv + po*								
Imaeda H 2011	8	62	9	61	7.2%	0.86 (0.31, 2.39)		
Lin HJ 1998	2	50	20	50	17.6%	0.06 (0.01, 0.29)		
Lin HJ (a) 2006	6	67	22	67	18.3%	0.20 (0.08, 0.54)		
Lin HJ (b) 2006	14	66	22	67	15.8%	0.55 (0.25, 1.20)		
Jeong HK 2007	3	85	10	79	9.2%	0.25 (0.07, 0.95)		
Hsu PI 2004	2	52	8	50	7.2%	0.21 (0.04, 1.04)		
Sakurada T 2012	1	40	2	37	1.9%	0.45 (0.04, 5.17)		
Tomita T 2012	5	77	5	79	4.2%	1.03 (0.29, 3.70)		
Subtotal (95%CI)		499		490	81.3%	0.35 (0.24, 0.52)		
Total events	41		98					

Heterogeneity: $\chi^2 = 13.70$, $df = 7$ ($P = 0.06$); $I^2 = 49\%$
Test for overall effect: $Z = 5.20$ ($P < 0.00001$)

Study or subgroup	PPI Events	PPI Total	H$_2$RA Events	H$_2$RA Total	Weight	Odds ratio M-H, fixed, 95%CI		Risk of Bias
1.1.2 *iv*								
Jensen DM 2006	5	72	11	77	9.1%	0.45 (0.15, 1.36)		
Subtotal (95%CI)		72		77	9.1%	0.45 (0.15, 1.36)		
Total events	5		11					

Heterogeneity: Not applicable
Test for overall effect: $Z = 1.42$ ($P = 0.16$)

Study or subgroup	PPI Events	PPI Total	H$_2$RA Events	H$_2$RA Total	Weight	Odds ratio M-H, fixed, 95%CI		Risk of Bias
1.1.3 *po*								
Ye BD 2006	0	41	0	41		Not estimable		
Uedo N 2007	4	66	11	64	9.6%	0.31 (0.09, 1.03)		
Subtotal (95%CI)		107		405	9.6%	0.31 (0.09, 1.03)		
Total events	4		11					

Heterogeneity: Not applicable
Test for overall effect: $Z = 1.91$ ($P = 0.06$)

	PPI Total		H$_2$RA Total	Weight	Odds ratio M-H, fixed, 95%CI
Total (95%CI)	678		672	100.0%	0.36 (0.25, 0.51)
Total events	50	120			

Heterogeneity: $\chi^2 = 13.86$, $df = 9$ ($P = 0.13$); $I^2 = 35\%$
Test for overall effect: $Z = 5.70$ ($P < 0.00001$)
Test for subgroup differences: $\chi^2 = 0.22$, $df = 2$ ($P = 0.90$); $I^2 = 0\%$

0.01 0.1 1 10 100
Favours [PPI]   Favours [H$_2$RA]

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 2 Forest plot and risk of bias summary from the Cochrane risk of bias tool comparing proton pump inhibitors therapy *vs* H$_2$ receptor antagonists therapy efficacy for the recurrent bleeding rate. PPI: Proton pump inhibitors; H$_2$R: H$_2$ receptor antagonists.

and did observe a statistically significant difference (OR = 0.45; 95%CI: 0.15-1.36; Figure 2). Meanwhile, no statistical difference was observed in two trials[14,18] that reported the re-bleeding number after simple oral treatment (OR = 0.31; 95%CI: 0.09-1.03; Figure 2). The meta-analysis results for re-bleeding rate revealed that after successful endoscopic therapy, compared with the H$_2$RA therapy group, the PPI therapy group had significantly reduced re-bleeding rates (OR = 0.36; 95%CI: 0.25-0.51; Figure 2). Figure 2 shows the quality assessments of these ten articles, as evaluated by the Cochrane Collaboration's tool.

Inconsistencies within the end-point time, nationality and intervention drugs, may have resulted in significant and substantial heterogeneity in our analysis (Table 2). The first subgroup analysis used the time of recurrent bleeding occurrence after successful endoscopic therapy (d). Only one trial[17] reported the

re-bleeding number within 24 h and two trials[15,22] reported the re-bleeding number within 3 d. These trials were significantly heterogeneous in reducing the re-bleeding rate (OR = 0.23; 95%CI: 0.07-0.76; Table 2). An additional two trials[15,17] reported the re-bleeding number within 7 d after successful endoscopic therapy and observed a statistically significant reduction in the re-bleeding rate (OR = 0.32; 95%CI: 0.13-0.79; Table 2). Furthermore, heterogeneity was observed in the three trials[16,17,22] that reported the re-bleeding number within 14 d (OR = 0.26; 95%CI: 0.16-0.43; Table 2). Meanwhile, a statistical difference was observed in two trials[14,15] that reported the re-bleeding number within 28-30 days (OR = 0.45; 95%CI: 0.15-1.36; Table 2). Finally, there were five trials[13,18-21] that reported re-bleeding number within 6 wk or more and no statistical difference was observed (OR = 0.53; 95%CI: 0.30-0.94; Table 2). In summary,

Table 2 Subgroup analyses of recurrent bleeding rate

	Number of studies	Number of subjects	OR (95%CI)	Heterogeneity within subgroups	Difference between subgroups
End-point time					
Overall	10	2076	0.33 (0.24-0.45)	No (P = 0.20, I^2 = 23%)	No (P = 0.42, I^2 = 0%)
24 h	1	164	0.08 (0.00-1.46)	NA	
3 d	2	249	0.23 (0.07-0.76)	Yes (P = 0.13, I^2 = 56%)	
7 d	2	313	0.32 (0.13-0.79)	No (P = 0.37, I^2 = 0%)	
14 d	3	464	0.26 (0.16-0.43)	Yes (P = 0.07, I^2 = 58%)	
28-30 d	2	231	0.45 (0.15-1.36)	NA	
6 wk or more	5	588	0.53 (0.30-0.94)	No (P = 0.42, I^2 = 0%)	
Nation					
Overall	10	1283	0.36 (0.25-0.51)	No (P = 0.13, I^2 = 35%)	No (P = 0.42, I^2 = 0%)
Japan	4	486	0.63 (0.33-1.17)	No (P = 0.51, I^2 = 0%)	
China	3	402	0.25 (0.14-0.42)	Yes (P = 0.06, I^2 = 59%)	
South Korea	2	246	0.25 (0.07-0.95)	NA	
United States	1	149	0.45 (0.15-1.36)	NA	
Intervention drug PPI					
Overall	8	1030	0.32 (0.21-0.48)	No (P = 0.13, I^2 = 37%)	No (P = 0.93, I^2 = 0%)
Omeprazole	5	615	0.32 (0.20-0.52)	Yes (P = 0.03, I^2 = 61%)	
Pantoprazole	3	415	0.31 (0.15-0.65)	No (P = 0.69, I^2 = 0%)	
Intervention drug H₂RA					
Overall	8	996	0.33 (0.22-0.48)	No (P = 0.14, I^2 = 36%)	No (P = 0.18, I^2 = 41.6%)
Cimetidine	3	430	0.27 (0.16-0.44)	Yes (P = 0.07, I^2 = 58%)	
Famotidine	3	315	0.85 (0.28-2.61)	No (P = 0.56, I^2 = 0%)	
Ranitidine	2	251	0.34 (0.14-0.85)	No (P = 0.45, I^2 = 0%)	

OR: Odds ratio; CI: Confidence interval; NA: Not applicable.

this subgroup analysis demonstrated that the end-point time after successful endoscopic therapy was not significantly different between studies (OR = 0.33; 95%CI: 0.20-0.45; Table 2) and subgroups (P = 0.42; Table 2).

The second subgroup analysis used the nationality of origin for each study. Four Japanese trials[18-21] had an OR = 0.63 (95%CI: 0.33-1.17; Table 2) and did not demonstrate a statistically significantly reduced re-bleeding rate. Three Chinese trials[13,16,22] showed heterogeneity for reducing the re-bleeding rate (OR = 0.25; 95%CI: 0.14-0.42; Table 2). Two South Korea trials[14,17] and one United States trial[15] had an OR of 0.25 (95%CI: 0.07-0.95; Table 2) and 0.45 (95%CI: 0.15-1.36; Table 2), respectively. In summary, in this subgroup analysis for re-bleeding, the nationality of the study did not significant effect drug use after successful endoscopic therapy between the different studies (OR = 0.36; 95%CI: 0.25-0.51; Table 2) and subgroups (P = 0.42; Table 2).

The third subgroup analysis used groupings by the PPI intervention drug type. Five trials[14,16,19,20,22] used omeprazole as the intervention PPI drug and had significant heterogeneity, with an OR of 0.32 (95%CI: 0.20-0.52; Table 2). These five trials were not statistically significantly different compared with the three pantoprazole studies[13,15,17] (OR = 0.31, 95%CI: 0.15-0.65; Table 2). The fourth subgroup used groupings by the H₂RA intervention drug type. Three trials used cimetidine[16,18,22] as the H₂RA intervention drug and had an OR of 0.27 (95%CI: 0.16-0.44; Table 2) with significant heterogeneity. Three trials used

famotidine[14,20,21] as the H₂RA intervention drug (OR = 0.85; 95%CI: 0.28-2.61; Table 2) and two trials[13,15] used ranitidine as the H₂RA intervention drug (OR = 0.34; 95%CI: 0.14-0.85; Table 2). In summary, the H₂RA intervention drug subgroup analysis for the re-bleeding rate revealed that the H₂RA drug type after successful endoscopic therapy drug use had no significant effect in reducing the re-bleeding rate (OR = 0.33; 95%CI: 0.22-0.48; Table 2) or between subgroups (P = 0.18; Table 2).

In general, the subgroup analyses results did not reveal statistically significant differences in patients with upper gastrointestinal bleeding after successful endoscopic therapy (Table 2).

Use of PPI therapy compared with H₂RA therapy for mortality

Five studies[13,15-17,22], involving 715 patients, reported mortality after treatment. According to the different routes of administration, the studies could also be divided into three subgroups, intravenous followed by oral, simple intravenous and simple oral. There was no significant heterogeneity between these trials (P = 0.68, I^2 = 0%) or subgroups (P = 0.22, I^2 = 33.3%); therefore, we used a fixed effects model for the analysis. Four of the studies[13,16,17,22], including 588 subjects, used the first method, intravenous and then oral administration, and the mortality was not statistically significantly reduced (OR = 0.29; 95%CI: 0.08-0.17; Figure 3). Only one trial[15], including 149 subjects, reported the dead number after simple intravenous treatment and no statistically significant
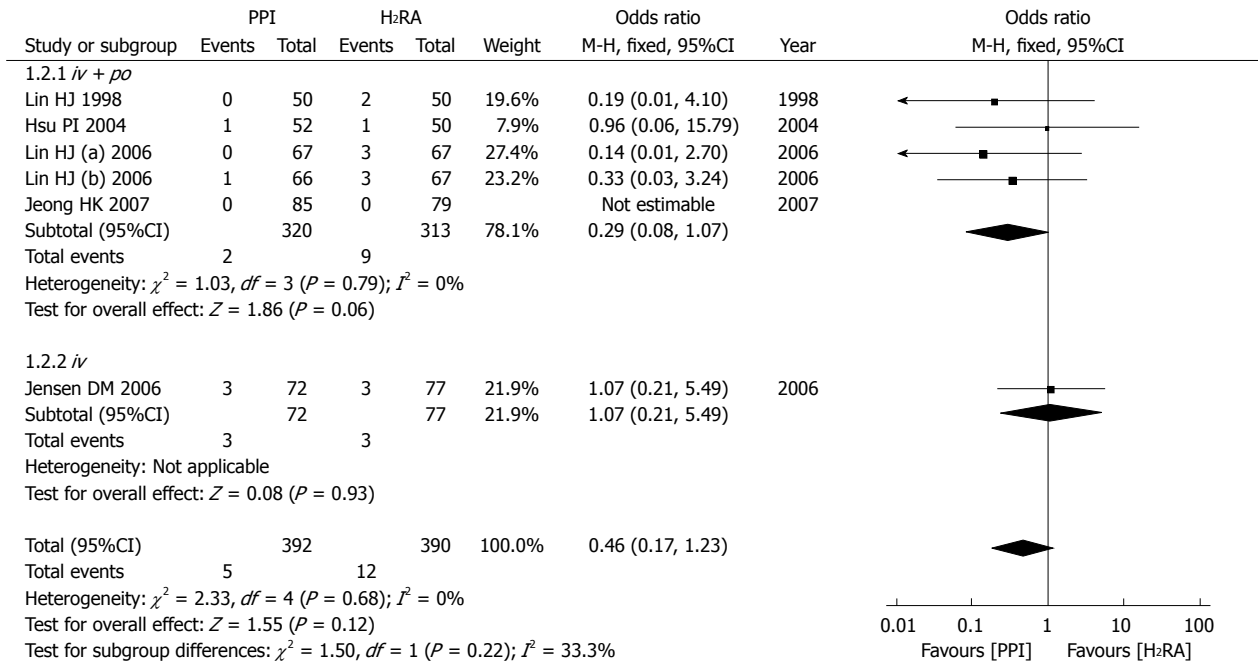
Study or subgroup	PPI Events	PPI Total	H₂RA Events	H₂RA Total	Weight	Odds ratio M-H, fixed, 95%CI	Year	Odds ratio M-H, fixed, 95%CI
1.2.1 *iv + po*								
Lin HJ 1998	0	50	2	50	19.6%	0.19 (0.01, 4.10)	1998	
Hsu PI 2004	1	52	1	50	7.9%	0.96 (0.06, 15.79)	2004	
Lin HJ (a) 2006	0	67	3	67	27.4%	0.14 (0.01, 2.70)	2006	
Lin HJ (b) 2006	1	66	3	67	23.2%	0.33 (0.03, 3.24)	2006	
Jeong HK 2007	0	85	0	79		Not estimable	2007	
Subtotal (95%CI)		320		313	78.1%	0.29 (0.08, 1.07)		
Total events	2		9					

Heterogeneity: $\chi^2 = 1.03$, $df = 3$ ($P = 0.79$); $I^2 = 0\%$
Test for overall effect: $Z = 1.86$ ($P = 0.06$)

Study or subgroup	PPI Events	PPI Total	H₂RA Events	H₂RA Total	Weight	Odds ratio M-H, fixed, 95%CI	Year	Odds ratio M-H, fixed, 95%CI
1.2.2 *iv*								
Jensen DM 2006	3	72	3	77	21.9%	1.07 (0.21, 5.49)	2006	
Subtotal (95%CI)		72		77	21.9%	1.07 (0.21, 5.49)		
Total events	3		3					

Heterogeneity: Not applicable
Test for overall effect: $Z = 0.08$ ($P = 0.93$)

Total (95%CI)		392		390	100.0%	0.46 (0.17, 1.23)		
Total events	5		12					

Heterogeneity: $\chi^2 = 2.33$, $df = 4$ ($P = 0.68$); $I^2 = 0\%$
Test for overall effect: $Z = 1.55$ ($P = 0.12$)
Test for subgroup differences: $\chi^2 = 1.50$, $df = 1$ ($P = 0.22$); $I^2 = 33.3\%$

Scale: 0.01 0.1 1 10 100 — Favours [PPI] / Favours [H₂RA]

Figure 3 Forest plot comparing the efficacy of proton pump inhibitors therapy *vs* H₂ receptor antagonists therapy for the recurrent bleeding rate mortality. PPI: Proton pump inhibitors; H₂R: H₂ receptor antagonists.

Study or subgroup	PPI Events	PPI Total	H₂RA Events	H₂RA Total	Weight	Odds ratio M-H, fixed, 95%CI	Year	Odds ratio M-H, fixed, 95%CI
Lin HJ 1998	0	50	0	50		Not estimable	1998	
Hsu PI 2004	0	52	1	50	13.2%	0.31 (0.01, 7.90)	2004	
Lin HJ (a) 2006	0	67	3	67	30.3%	0.14 (0.01, 2.70)	2006	
Lin HJ (b) 2006	0	66	3	67	30.1%	0.14 (0.01, 2.74)	2006	
Jeong HK 2007	2	85	3	79	26.5%	0.61 (0.10, 3.75)	2007	
Total (95%CI)		320		313	100.0%	0.29 (0.09, 0.96)		
Total events	2		10					

Heterogeneity: $\chi^2 = 1.14$, $df = 3$ ($P = 0.77$); $I^2 = 0\%$
Test for overall effect: $Z = 2.02$ ($P = 0.04$)

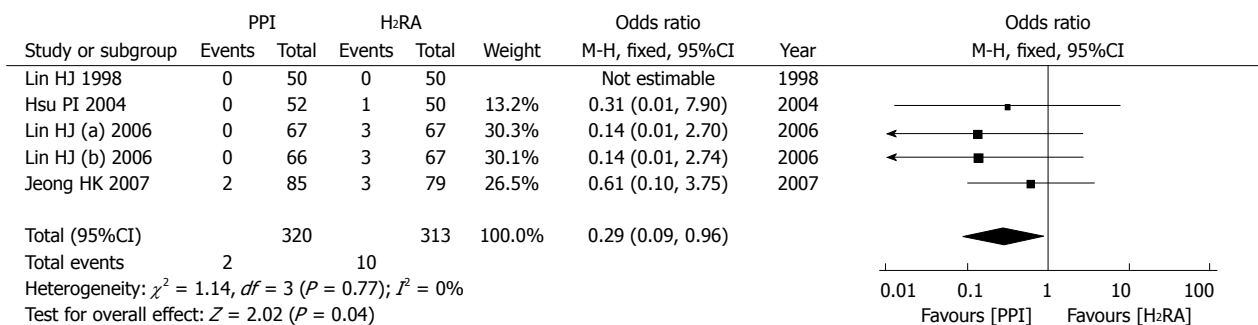Scale: 0.01 0.1 1 10 100 — Favours [PPI] / Favours [H₂RA]

Figure 4 Forest plot comparing the efficacy of proton pump inhibitors therapy *vs* H₂ receptor antagonists therapy for the required surgery rate. PPI: Proton pump inhibitors; H₂R: H₂ receptor antagonists.

difference was observed (OR = 1.07; 95%CI: 0.21-5.49; Figure 3). In summary, this meta-analysis of mortality revealed that after successful endoscopic therapy, there were no significant differences in mortality between the two drugs (OR = 0.46; 95%CI: 0.17-1.23; Figure 3).

Use of PPI therapy compared with H₂RA therapy in the receiving required surgery rate

Four studies[13,16,17,22], involving 566 patients, reported the number of patients who received surgery after treatment. There was no significant heterogeneity between these trials ($P = 0.77$, $I^2 = 0\%$); therefore, a fixed effects model was used for the analysis. The meta-analysis revealed that after successful endoscopic therapy, compared with H₂RA therapy, PPI therapy significantly decreased the number of patients that received surgery (OR = 0.29; 95%CI: 0.09-0.96; Figure 4).

Use of PPI therapy compared with H₂RA therapy for blood transfusion amounts (units)

Three studies[13,16,22], involving 402 patients, reported the units (mL; 500 mL per unit) for patients who required blood transfusions after treatment. There was significant heterogeneity between these trials ($P = 0.0001$, $I^2 = 89\%$); therefore, a random effects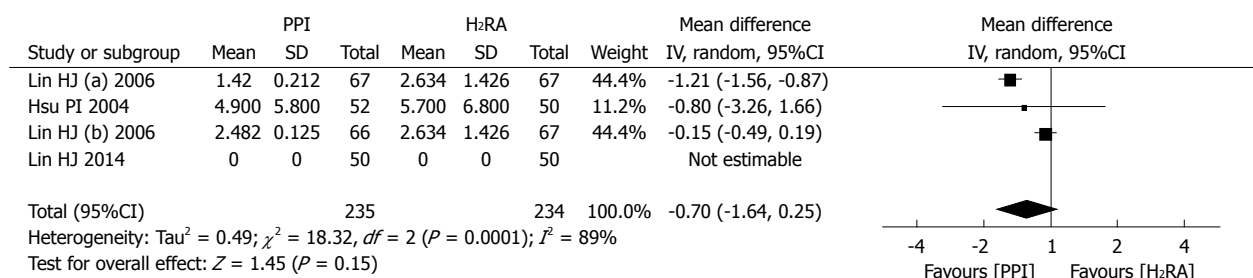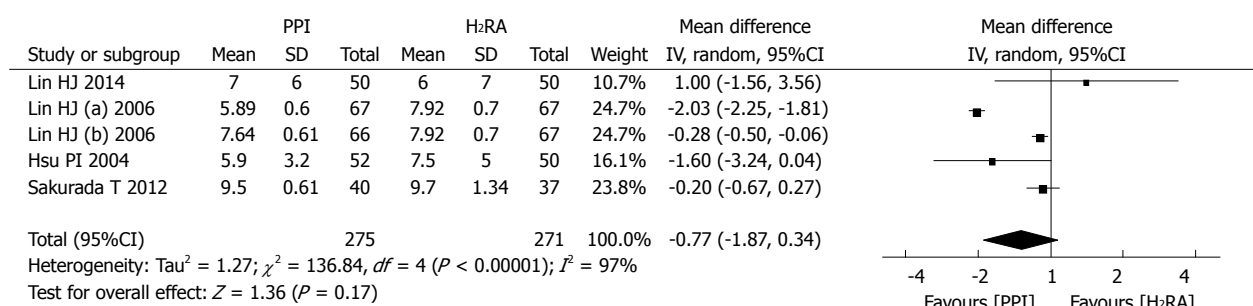 model was used for the analysis. The meta-analysis revealed that after successful endoscopic therapy, PPI therapy was more effective in decreasing blood transfusion units (WMD: -0.70 unit; 95%CI:-1.64-0.25; Figure 5).

Use of PPI therapy compared with H₂RA therapy for hospitalization time (days)

Four studies[13,16,20,22], involving 479 patients, reported the hospitalization time of patients. There was significant heterogeneity between these trials ($P < 0.00001$, $I^2 = 97\%$); therefore, a random effects model was used for the analysis. The meta-analysis revealed

Study or subgroup	PPI			H₂RA			Weight	Mean difference IV, random, 95%CI	Mean difference IV, random, 95%CI
	Mean	SD	Total	Mean	SD	Total			
Lin HJ (a) 2006	1.42	0.212	67	2.634	1.426	67	44.4%	-1.21 (-1.56, -0.87)	
Hsu PI 2004	4.900	5.800	52	5.700	6.800	50	11.2%	-0.80 (-3.26, 1.66)	
Lin HJ (b) 2006	2.482	0.125	66	2.634	1.426	67	44.4%	-0.15 (-0.49, 0.19)	
Lin HJ 2014	0	0	50	0	0	50		Not estimable	
Total (95%CI)			235			234	100.0%	-0.70 (-1.64, 0.25)	

Heterogeneity: Tau² = 0.49; χ^2 = 18.32, *df* = 2 (*P* = 0.0001); I^2 = 89%
Test for overall effect: *Z* = 1.45 (*P* = 0.15)

Figure 5 Forest plot comparing the efficacy of proton pump inhibitors therapy *vs* H₂ receptor antagonists therapy for blood transfusion units. PPI: Proton pump inhibitors; H₂R: H₂ receptor antagonists.

Study or subgroup	PPI			H₂RA			Weight	Mean difference IV, random, 95%CI	Mean difference IV, random, 95%CI
	Mean	SD	Total	Mean	SD	Total			
Lin HJ 2014	7	6	50	6	7	50	10.7%	1.00 (-1.56, 3.56)	
Lin HJ (a) 2006	5.89	0.6	67	7.92	0.7	67	24.7%	-2.03 (-2.25, -1.81)	
Lin HJ (b) 2006	7.64	0.61	66	7.92	0.7	67	24.7%	-0.28 (-0.50, -0.06)	
Hsu PI 2004	5.9	3.2	52	7.5	5	50	16.1%	-1.60 (-3.24, 0.04)	
Sakurada T 2012	9.5	0.61	40	9.7	1.34	37	23.8%	-0.20 (-0.67, 0.27)	
Total (95%CI)			275			271	100.0%	-0.77 (-1.87, 0.34)	

Heterogeneity: Tau² = 1.27; χ^2 = 136.84, *df* = 4 (*P* < 0.00001); I^2 = 97%
Test for overall effect: *Z* = 1.36 (*P* = 0.17)

Figure 6 Forest plot comparing the efficacy of proton pump inhibitors therapy *vs* H₂ receptor antagonists therapy for hospitalization time. PPI: Proton pump inhibitors; H₂R: H₂ receptor antagonists.

Figure 7 Funnel plot evaluating the publication bias for recurrent bleeding rate.

that after successful endoscopic therapy, PPI therapy was more effective in decreasing hospitalization time (WMD: -0.77d; 95%CI: -1.87-0.34; Figure 6).

Publication bias assessment
Publication bias was evaluated using a Funnel plot (Figure 7). The asymmetrical scatter plot revealed little publication bias in our meta-analysis. In addition, we also performed the Begg's test and Egger's test; both tests demonstrated that there was no publication bias in our meta-analysis (Begg's test: *P* = 0.283; Egger's test: *P* = 0.339).

DISCUSSION
In patients with upper gastrointestinal bleeding after

successful endoscopic therapy, compared with H₂RA therapy, PPI therapy was more effective for reducing the re-bleeding rate and received surgery rate, but there were no significant differences in mortality between the two drugs. There was little heterogeneity between the three different methods of administration (*iv* + *po*; *iv*; *po*). The results also revealed that intravenous and oral PPI had similar results, which has also been proposed by several published studies[23,24], and the PPI therapeutic results were more effective than H₂RA therapy. In this meta-analysis, the intravenous followed by oral administration method had better therapeutic value than either simple intravenous therapy or simple oral therapy, which may prompt a standard drug administration method.

For the subgroup analyses of the re-bleeding time, the risk of recurrent bleeding was highest during the first 3 d after therapy and most re-bleeding events occurred in the first 24 h[6]. In this meta-analysis, we concluded that PPI can significantly reduce the re-bleeding rate during the first 3 d after successful endoscopic therapy compared with H₂RA. Additionally, the same result was observed during 7 d and 14 d post endoscopy, which indicated that PPI can decrease the short-term re-bleeding rate. Furthermore, the same result was observed in the group of studies that evaluated 6 wk or more post endoscopy, which illustrated that PPIs may also decrease the long-team re-bleeding rate. However, in the 28-20 d group, the two types of drugs produced similar results, with an OR < 1 (OR = 0.45, Table 2), which indicated that PPI therapy tends to be better than H₂RA therapy.

There was no significant difference between the different populations included in the studies in our meta-analysis ($P = 0.16$, $I^2 = 41.2\%$, Table 2); therefore, we concluded that in patients with upper gastrointestinal bleeding after successful endoscopic therapy, PPI has better therapeutic value worldwide. However, a meta-analysis by Leontiadis *et al*[25] revealed that PPI therapy for ulcer bleeding was more efficacious in Asia than elsewhere, which conflicts with the results in our study. However, in our meta-analysis, nine out of ten studies were conducted in Asian countries, which may result in geographical limitations.

In the subgroup analysis of PPI type, there was no significant difference between the omeprazole group and pantoprazole group ($P = 0.93$, $I^2 = 0\%$, Table 2); *i.e.*, the different PPI types had little influence on outcome. However, in the analysis of the H2RA group, although there was no heterogeneity difference between the groups ($P = 0.18$, $I^2 = 41.6\%$, Table 2), cimetidine and ranitidine had superior curative effects compared with famotidine (Table 2).

The standard dose of PPI used after successful endoscopic therapy is hard to determine, the included studies showed large differences in the dose administered; however, the meta-analysis of Wu *et al*[26] demonstrated that low-dose intravenous PPI can achieve the same efficacy as high-dose PPI following endoscopic hemostasis. To clarify these conclusions, additional research must be conducted.

In the ten included studies, there were no serious adverse reactions. An evaluation of the acute and chronic adverse reactions of PPIs and H2RAs is necessary because the treatment period ranged from 3 d to a few weeks. The results suggested that these two types of drugs have short-term adverse reactions that are mild or not obvious. PPIs are a well-tolerated pharmaceutical class, with adverse effects occurring at a rate of 1%-3%, and with no significant differences between PPI types[27]. The adverse effects most commonly observed with PPI use are nausea, rash, headaches, constipation, flatulence, diarrhea, abdominal pain and dizziness[28]. However, in patients with a history of ulcer bleeding, long-term oral PPI is necessary and the safety of long-term PPI use is controversial. Insogna *et al*[29] revealed that long-term PPI use may influence mineral metabolism, specifically calcium absorption, which increased the risk of bone fracture. Ito *et al*[30] demonstrated that long-term PPI use may influence calcium absorption, as well as influence the absorption of vitamin B_{12}, iron and magnesium, which can have important clinical implications. However, tolerance has been reported to prolonged H2RA therapy, as discussed in several studies. Rackoff *et al*[31] argued that prolonged hypergastrinemia is induced by long-term or high dose H2RA therapy.

There were several limitations in this study. First, the quality of the included randomized controlled trials was variable, but most of them were of acceptable quality. A number of high-quality, well-designed RCTs are needed for further research. Future studies should describe the grouping method in detail and disclose the number of patients lost to follow-up and exit. Second, heterogeneity between the studies may have skewed the meta-analysis results; the results may be from the baseline and after pharmaceutical therapy. For example, in our meta-analysis, the baseline values of the smoking rate, alcohol abuse rate, positive *H. pylori* infection rate and NSAID use rate in the included studies were different and these factors may have affected the analysis results. Additionally, the agents used in the included studies were different; most studies used pantoprazole or omeprazole for the PPI group, whereas cimetidine, famotidine and ranitidine were mostly used in the H2RA group. Some factors were influenced by the area, hospital, *etc.*, particularly the mean hospitalization days. Therefore, subject enrollment data should include age, sex, risk and drug types, as well as, follow-up time, endpoint and the number of patients who accepted PPI therapy or H2RA therapy. Third, the potential for publication bias is always a concern. The number of included studies and differences in sample size may have affected the publication bias. Fourth, it is difficult to publish the results when the results do not identify any significant differences, *i.e.*, PPI therapy has similar efficacy to H2RA therapy. This phenomenon may have led to bias.

Further research, specifically large-scale double-blind randomization trials, are required to provide more credible data for PPI or H2RA treatment using different administration methods in upper gastrointestinal bleeding patients.

COMMENTS

Background
In patients with upper gastrointestinal bleeding, recurrent bleeding is the most important adverse effect, resulting in morbidity and mortality. Both proton pump inhibitors and H2 receptor antagonists are commonly administered to upper gastrointestinal bleeding patients after successful endoscopic therapy.

Research frontiers
A series of randomized controlled trials were conducted to compare proton pump inhibitor (PPI) therapy and H2 receptor antagonists (H2RA) therapy after successful endoscopy to determine the appropriate first-line treatment drug for upper gastrointestinal bleeding.

Innovations and breakthroughs
This is the first meta-analysis to evaluate the efficacy and safety of PPI therapy and H2RA therapy after successful endoscopy in patients with upper gastrointestinal bleeding, using several important endpoints, such as rebleeding rate, mortality and receiving surgery rate.

Applications
The results suggested that PPI therapy is superior to H2RA therapy in upper gastrointestinal bleeding patients after successful endoscopic therapy. This result may provide valuable information to clinicians.

Terminology
PPI is a type of H^+/K^+ ATPase inhibitor. Its acid-suppressing activity is potent, highly specific and has a long duration. H2RA can selectively block wall H2 receptors on the cell membrane, reducing gastric acid secretion.

Peer-review
This is a well-performed meta-analysis that aimed to determine whether PPI therapy is more efficacious and safe than H2RA therapy in upper gastrointestinal bleeding patients after successful endoscopic therapy that provides definitive

results.

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