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Cost-effectiveness and clinical outcomes of intermittent/continuous proton pump inhibitors infusion in high bleeding risk of ulcers

A retrospective observational cohort study

Hui-Hsia Hsieh, MSc[a,b], Tien-Yuan Wu, PhD[a,c], Chi-Hua Chen, MSc[a], Mann-Jen Hour, PhD[b,*]

Abstract

The purpose of this study was to evaluate the clinical outcomes, including patient prognosis and medication expense, of proton pump inhibitors administered by high-dose continuous infusion (HDC, 80 mg loading dose, then 8 mg/h for 72 hours) or non-high-dose intermittent infusion (NHDI, 40 mg qd or 40 mg q12 h, for 3 days) regimens in high-risk patients with bleeding peptic ulcers.

In this retrospective cohort study, patients with peptic ulcers and endoscopic hemostasis between January, 2013 and December, 2015 were included. The primary endpoints were rebleeding and mortality rates within 7 days. The secondary endpoints were length of stay (LOS), transfusion units of packed red blood cells (PRBCs), and the number needed to treat.

A total of 335 patients met the inclusion criteria during the 3-year follow-up period. The cumulative incidence of rebleeding within 7 days was 20.4% and 11.2% in the HDC and NHDI groups, respectively, with a significant difference ($P = .021$). The mortality rate was 12.1% and 7.3% in the HDC and NHDI groups, respectively, with no significant difference ($P = .136$). Univariate Cox proportional hazards model analysis showed that the risk of rebleeding within 7 days in the HDC group was higher than that in the NHDI group. The hazard ratio for HDC vs. NHDI was 1.93 ($P = .021$). There were significant differences in LOS ($P = .034$) and PRBC units ($P = .005$) for risk of rebleeding within 7 days, as well as in transfusion units of PRBCs for mortality rate analysis ($p < 0.001$), between the HDC and NHDI groups. The results showed that the NHDI regimen could reduce the risk of rebleeding within 7 days in 1 of 11 patients (number needed to treat = 11) and could reduce medication cost by US$ 400 to 800.

The NHDI regimen showed a lower risk of rebleeding within 7 days, shorter LOS, and fewer PRBC units than that of the HDC regimen. Receiving NHDI has better cost-effective outcomes than that of HDC for patients with high-risk bleeding peptic ulcers.

Abbreviations: CI = confidence interval, CV = cardiovascular, HDC = high-dose continuous infusion, HR = hazard ratio, LOS = length of stay, NHDI = non-high dose intermittent infusion, NNT = number needed to treat, NSAID = non-steroid anti-inflammatory drug, PPIs = proton pump inhibitors, PRBCs = packed red blood cells, UGIB = upper gastrointestinal bleeding.

Keywords: bleeding peptic ulcer, continuous proton pump inhibitors infusion, cost-effectiveness, intermittent proton pump inhibitors infusion

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1. Introduction

The incidence and overall mortality rate of acute upper gastrointestinal bleeding (UGIB) has an increasing trend due to the increasing number of elderly, non-steroidal anti-inflammatory drug (NSAID) users, and people with stressful lifestyles.[1] NSAIDs are well-known drugs that induce peptic ulcers. Cyclooxygenase inhibition in the gastrointestinal tract leads to reduced secretion of prostaglandins, which protect the gastric mucosa. Therefore, NSAIDs increase the susceptibility to mucosal injury.[2] Moreover, aspirin and clopidogrel as antiplatelet agents, which are critically important for the prevention of coronary stent thrombosis, have a substantially high risk of gastrointestinal complications, such as ulceration and related bleeding. Both NSAIDs and antiplatelet agents may induce peptic ulcers and related bleeding. Proton pump inhibitors (PPIs) are often prescribed prophylactically to antiplatelet agent receivers to reduce the risk of gastrointestinal tract bleeding.[3] The drug-drug interaction between clopidogrel and PPIs has become an important issue. Clopidogrel is a prodrug that requires bioactivation via cytochrome P450 enzymes, including a key determinant CYP2C19. The active metabolite irreversibly inhibits platelet ADP receptor P2Y12 to achieve the antiplatelet effect. Unfortunately, PPIs can inhibit CYP2C19 activity,

decreasing clopidogrel conversion to its active form, reducing its antiplatelet effect, and possibly increasing the occurrence of adverse cardiovascular events.[4] Endoscopy hemostasis is the first choice for treating upper gastrointestinal ulcers with active bleeding. Regarding the timing of endoscopy, US guidelines suggest that patients with higher-risk clinical features such as tachycardia, hypotension, and hematemesis should undergo endoscopic hemostasis within 12 h to improve prognosis.[5] In Taiwan, the guidelines suggest that patients with active bleeding, exposed blood vessels at the bottom of the ulcer, or red or black blood crust, such as Forrest I and Forrest II, should undergo endoscopic hemostasis within 24 to 48 hours. The commonly used endoscopic hemostasis treatment methods include injection hemostasis, thermocoagulation, and mechanical hemostasis. Patients ingesting anticoagulant drugs should stop the medications before undergoing the endoscopic regimen, confirm the coagulation function, and consult the cardiovascular expert.[6]

Peptic ulcers are the most common causes of UGIB. Approximately 80% of patients achieve hemostasis after endoscopic treatment; however, the remaining 20% of patients experience rebleeding.[7,8] Rebleeding is the most important factor affecting the prognosis of peptic ulcers. Therefore, effective prevention of peptic ulcer rebleeding is necessary. According to the therapeutic guidelines of the American College of Gastroenterology, patients with bleeding ulcers who have high-risk endoscopic findings (active bleeding, Forrest Ia; nonbleeding visible vessels, Forrest IIa; adherent clots, Forrest IIb) are recommended to receive PPIs following endoscopic treatment.[5] Patients classified as Forrest Ia, IIa, and IIb were reported to exhibit a significantly greater risk of rebleeding than Forrest Ib patients.[9] In the American College of Gastroenterology guideline, high-dose continuous infusion (HDC) of PPIs is recommended to prevent rebleeding.[5,10] Administering PPIs such as the HDC regimen (80 mg bolus followed by 8 mg/h for 72 h) and non-high dose intermittent infusion (NHDI) regimens (40 mg qd or 40 mg q12 h, for 3 days) to prevent recurrent gastrointestinal hemorrhage after endoscopic therapy is accepted worldwide.[11] The prophylactic effects of rebleeding are inconsistent or indistinguishable in these different regimens. Therefore, we aimed to evaluate the utilization of PPIs in high-risk of rebleeding ulcers, particularly to compare the clinical outcomes and medication expenses of HDC and NHDI regimens. We aimed to derive meaningful conclusions that could be recommended to effectively prevent rebleeding and economize the costs of health insurance.

2. Methods

2.1. Ethical approval

The study was approved by the Research Ethics Committee of Taichung Tzu Chi Hospital (REC105-28), and the requirement for informed consent was waived.

2.2. Study design and patient population

The 3-year retrospective cohort study was conducted from January, 2013 to December, 2015 at Taichung Tzu Chi Hospital, a regional teaching hospital in Taichung, Taiwan. The inclusion criteria were as follows: (1) patients with peptic ulcer-related diseases with International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 531.4–533.9 and 578.9; (2) patients who underwent endoscopic hemostasis treatment that accepted health insurance codes 47043B (upper digestive tract endoscopic hemostasis) and 47067B (endoscopic esophageal varices ligation); (3) age >20 years; (4) patients identified in Forrest classification stages Ia, Ib, IIa, or IIb. Treatment protocols were treated with HDC PPI regimen (80 mg loading dose then 8 mg/h for 72 h) or NHDI PPI regimen (40 mg QD or Q12H for 3 days). The exclusion criteria were those who underwent Forrest stages IIc and III.

The primary endpoints were rebleeding and mortality rates within 7 days. The secondary endpoints were length of stay (LOS), transfusion units of packed red blood cells (PRBCs), and the number needed to treat (NNT), which was measured to evaluate the cost and benefit of treatment.

2.3. Statistical analysis

Means, standard deviations, and *t*-tests are presented for normally distributed continuous variables. We used the Kolmogorov–Smirnov test to assess the normality of the distribution of continuous variables. Medians, interquartile ranges, and Wilcoxon–Mann–Whitney tests are presented for non-normally distributed continuous variables, and counts, percentages, and χ^2 tests are presented for categorical variables. The sample sizes and variables of the HDC and NHDI groups were calculated using G*Power v3.1 (Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany), and the power was higher than 0.9 in this study. Rebleeding and mortality rates within 7 days were further analyzed using Kaplan–Meier curves, and the independent risk factors for rebleeding were predicted by Cox proportional hazards model analysis. All selected variables included in the multivariate Cox proportional hazards model analysis were related to the clinical outcomes. Statistical analysis was performed using SAS v9.3 (SAS Institute Inc., Cary, NC) and SPSS v21 (IBM Corporation, Armonk, NY) statistical software. Statistical significance was set at $P < .05$.

3. Results

Between January, 2013 and December, 2015, 788 patients with ICD-9-CM codes of 531.4–533.9 and 578.9 underwent endoscopy for UGIB. Eventually, 335 patients (226 men and 109 women) met our criteria and were included in the study. Among them, 157 and 178 patients received the HDC and NHDI regimens, respectively (Fig. 1). In the Forrest classification Ia, 80% of patients received HDC and 20% of patients received the NHDI regimen. In addition, 56.6% vs. 43.4% in Forrest Ib, 34.5% vs. 65.5% in Forrest IIa, and 45.4% vs. 54.6% in Forrest IIb received the HDC and NHDI regimens, respectively (Table 1).

3.1. Primary endpoints

As shown in Figure 2, 20.4% of rebleeding occurs within 7 days in the HDC group vs. 11.2% in the NHDI group ($P = .021$, with a significant difference), and the mortality rate is 12.1% in the HDC group vs. 7.3% in the NHDI group ($P = .136$, without a significant difference). The causes of death included hypovolemic shock and septic shock. The mortality rate of hypovolemic shock was 84.2% in the HDC group vs. 69.2% in the NHDI group, and the mortality rate of septic shock was 15.8% in the HDC group vs. 30.8% in the NHDI group ($P = .401$, without a significant difference; Table 1). Kaplan–Meier analysis revealed that there

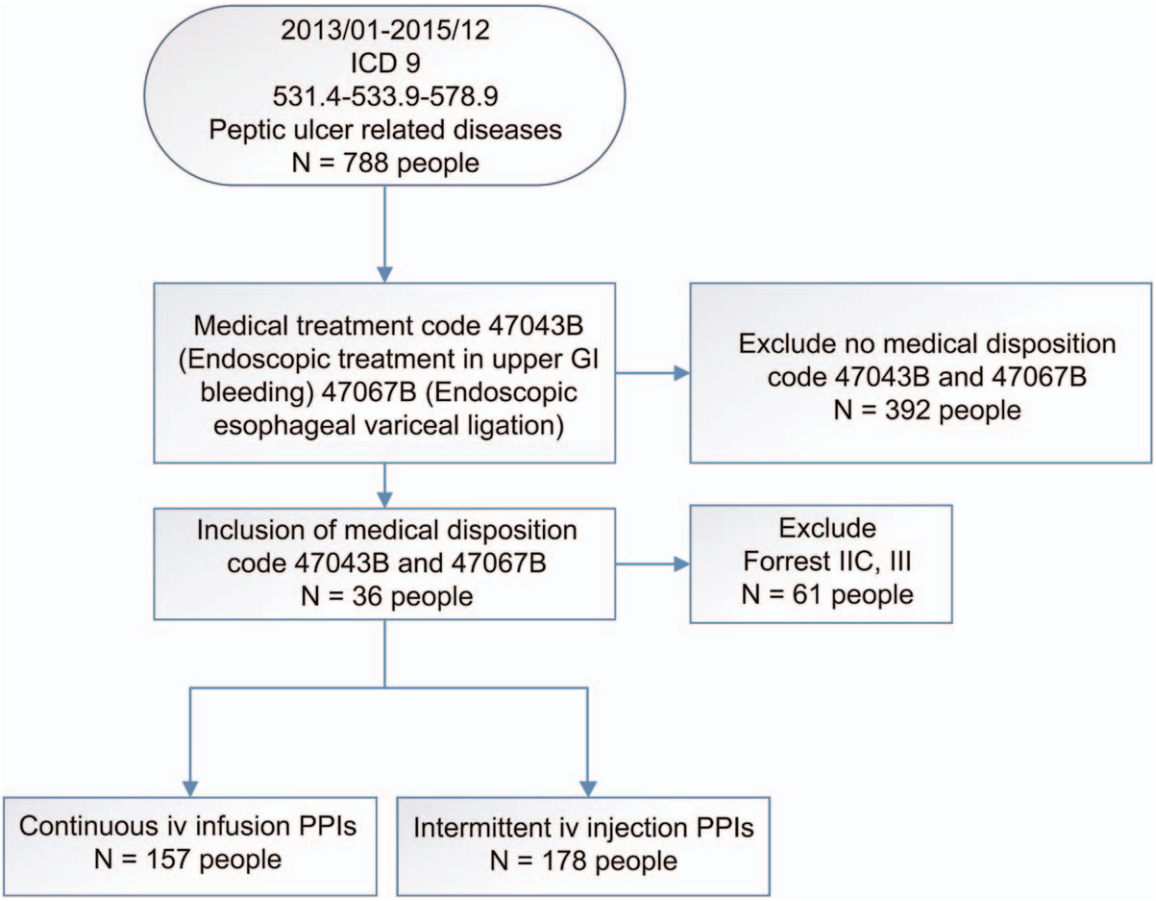

Figure 1. Study flow diagram.

Table 1

Basic information of patients recruited in this study.

Characteristics	HDC (n = 157)*	NHDI (n = 178)*	*P* value†
Mean age, yr	68 ± 12	70 ± 13	.967
ICU	62 (39.5%)	36 (20.2%)	<.001
PRBC	5.1 ± 4.5	3.5 ± 3.1	<.001
Hb	7.9 ± 1.7	8.4 ± 1.8	.019
Length of stay	8.6 ± 4.1	7.0 ± 3.3	<.001
Forrest classification			<.001
Ia	16 (80.0%)	4 (20.0%)	
Ib	56 (56.6%)	43 (43.4%)	
IIa	41 (34.5%)	78 (65.5%)	
IIb	44 (45.4%)	53 (54.6%)	
Drugs status			.083
Esomeprazole	85 (54.1%)	113 (63.5%)	
Pantoprazole	72 (45.9%)	65 (36.5%)	
Rebleeding event	32 (20.4%)	20 (11.2%)	.021
Mortality event	19 (12.1%)	13 (7.3%)	.136
Hypovolemic shock	16 (84.2%)	9 (69.2%)	.401‡
Septic shock	3 (15.8%)	4 (30.8%)	

HDC = high-dose continuous infusion, PRBCs = packed red blood cells.
* Data are presented as mean ± SD or number (%).
† Continuous variables: Student *t*-test.
‡ Categorical variables: χ^2 test or The Fisher exact test.

were statistically significant differences between the two groups regarding rebleeding within 7 days (Fig. 3), and no significant differences in mortality rates (Fig. 4). The univariate Cox proportional hazards model used the NHDI group as a reference to analyze rebleeding within 7 days. The risk of rebleeding within 7 days in the HDC group was higher than that in the NHDI group. The hazard ratio (HR) for HDC vs. NHDI was 1.93 (95% confidence interval [CI], 1.10–3.37, $P = .021$).

3.2. Secondary endpoints

The multivariate Cox proportional hazards model was conducted with LOS, PRBC units, and hemoglobin level as controlled variables. As for rebleeding risk within 7 days, the results showed significant differences in the LOS (HR, 1.07; 95% CI, 1.01–1.15; $P = .034$; Fig. 5) and PRBC units (HR, 1.11; 95% CI, 1.03–1.20; $P = .005$; Fig. 5). The overall rebleeding risk in the HDC group was higher than that in the NHDI group, however, there was no significant difference (HR, 1.33; 95% CI, 0.73–2.4; $P = .35$; Fig. 5). As for mortality rate, there was a significant difference in PRBCs units used for transfusion (HR, 1.23; 95% CI, 1.14–1.33; $P < .001$; Fig. 5). The overall difference between the HDC and NHDI groups was not significantly different (HR, 0.94; 95% CI, 0.43–2.08; $P = .887$; Fig. 5).

The absolute risk reduction rate was 9.2%, and the NNT was 11. NHDI therapy reduced the risk of rebleeding within 7 days in

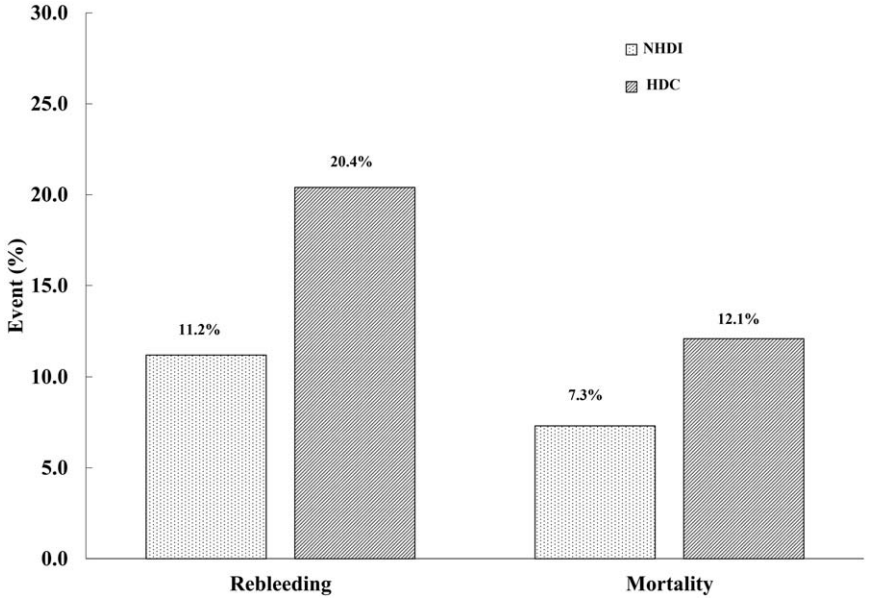

Figure 2. Rebleeding and mortality rate within 7 days. Rebleeding occurred within 7 days was 20.4% and 11.2% of patients ($P = .021$, significant difference), and the mortality rate was 12.1% and 7.3% in the HDC and NHDI groups, respectively ($P = .136$, no significant difference).

1 of 11 patients. The cost of the 3-day treatment was lower in the NHDI group than in the HDC group (US$ 33–67 saved). Every 11 patients (NNT = 11) using the NHDI regimen of PPIs could save US$ 400–800 of medication cost, and the risk of rebleeding could be reduced in one patient within 7 days (Table 2). In terms of hospital stays, the LOS was 7.03 days/patient in the NHDI group vs. 8.59 days/patient in the HDC group. Thus, every patient's hospitalization cost in the NHDI group could be reduced by the expense of 1.56 days. The daily hospitalization cost (estimated US$ 100/day for a single room) yielded a total savings of approximately US$ 156 per patient. Regarding PRBCs transfusion costs, the total transfusion volume of PRBCs in the NHDI group was 3.46 units/patient vs. 5.11 units/patient in the HDC group. Approximately 1.65 units of PRBCs (US$ 15.83/unit) yielded a total savings of approximately US$ 26.12 per patient for PRBC blood transfusion. Overall, the NHDI regimen was better than the HDC regimen of PPIs in terms of cost and benefit.

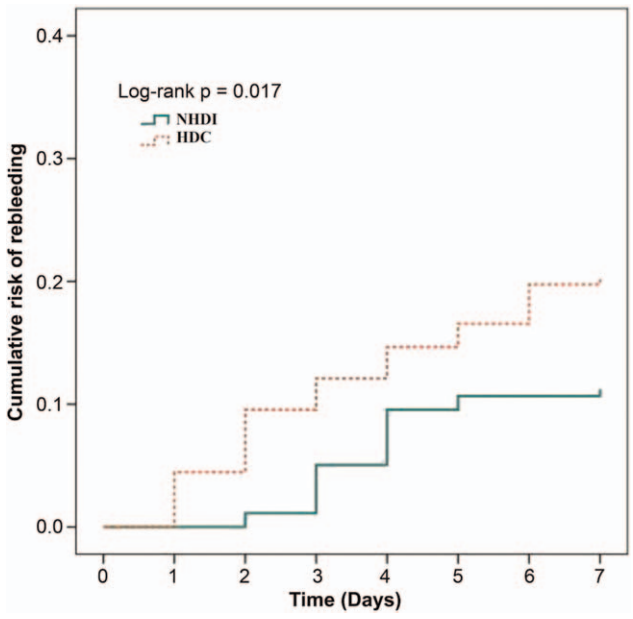

Figure 3. Kaplan–Meier failure curves of re-bleeding risk stratified by HDC versus NHDI status.

We further observed that 10.3% of *Helicobacter pylori* (*H pylori*) positive patients vs. 11.4% of *H pylori*-negative patients experienced rebleeding within 7 days (χ^2 tests, $p = 1$, with no significant difference). Adverse events and drug-drug interactions that occurred during PPI therapy were also evaluated. In our study, a total of 335 patients received NHDI or HDC PPI therapy; however, 32 patients died during therapy and only 303 patients converted to oral PPIs for maintenance therapy, in which only 2 of 23 patients (8.7%) who used PPIs for more than a year had an adverse fracture event (Table 3). In maintenance therapy, 47 patients were concomitantly administered oral PPIs and clopidogrel. Among them, 2 of 5 patients (40%) with combined clopidogrel and esomeprazole experienced cardiovascular (CV) adverse events, 2 of 8 patients (25%) with combined lansoprazole experienced CV events, and the remaining 34 patients with combined pantoprazole or rabeprazole did not experience CV events. The results showed that clopidogrel combined with esomeprazole or lansoprazole was associated with a higher risk of CV events ($P = .025$; Table 3).

4. Discussion

A medical team from the National Taiwan University conducted a meta-analysis on high-risk peptic ulcer bleeding patients in 2010 and showed that the HDC PPI regimen did not improve patient outcomes, including rebleeding rate, surgical rate, or mortality.[12] In agreement with the previous study, the current results of our study showed a similar finding.

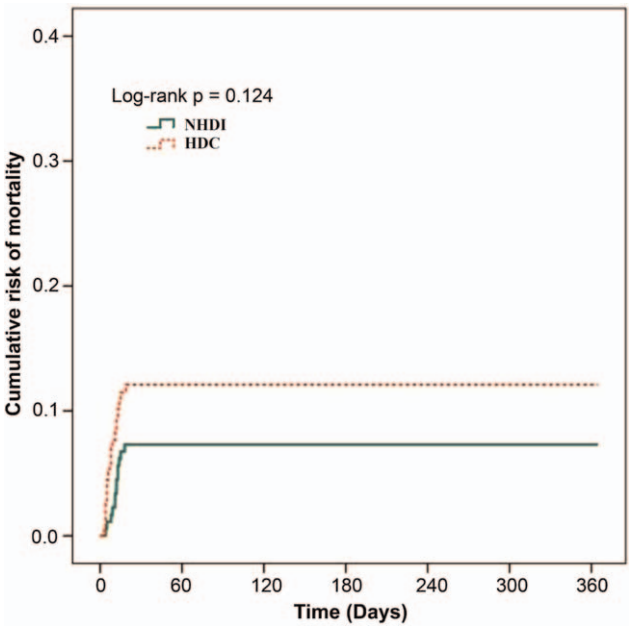

Figure 4. Kaplan–Meier failure curves of mortality risk stratified by HDC versus NHDI status.

Choi et al reported greater effectiveness in *H pylori*-infected peptic ulcer patients than in *H pylori*-uninfected patients receiving the same dose of PPI therapy.[13] Other studies revealed that peptic ulcer bleeding patients without *H pylori* infection have higher mortality and rebleeding rates,[14,15] however, the results of our study did not demonstrate that *H pylori* infection was an independent risk factor for rebleeding. This result may be due to insufficient sample size or low detection rate (57.3%) of *H pylori* infection. Our statistical results were not significantly different between the *H pylori*-positive and *H pylori*-negative groups.

Table 2

Cost analysis of HDC and NHDI regimen.

Drug	A* Cost of HDC (US$)	B† Cost of NHDI (US$)	B-A	(B-A)xNNT
Esomeprazole§	44.77	(1) 7.90	−36.87	−405.53
Pantoprazole¶	87.27	(1) 15.40	−71.87	−790.53
		(2) 30.80	−56.47	−621.13

HDC = high-dose continuous infusion, NHDI = non-high dose intermittent infusion.
* A = Continuous infusion: 80 mg bolus followed by 8 mg/h for 72 hours.
† B = Intermittent infusion: (1) 40 mg qd for 3 day, (2) 40 mg q12 h for 3 days.
§,¶ The National Health Insurance price of Esomeprazole 40 mg/vial and Pantoprazole 40 mg/vial is US $ 2.63 and $5.13 respectively.

Whether long-term PPI use may increase fracture risk remains a controversial issue, because of the inconsistency in clinical research results. In 2011, an observational study surveyed 10 previously published studies and found that there was a moderate association between PPI use and the increased risk of hip and spinal fractures.[16] In 2016, Targownik et al demonstrated that long-term use (≥5 years) of PPI did not increase the risk of fracture; furthermore, it was unrelated to changes in bone mineral density and bone strength.[17] There was also no causal relationship between PPI administration and fracture risk in our study. (Table 3).

A systematic review and meta-analysis published in 2017 discussed whether the combination of clopidogrel and PPIs could increase adverse reactions in patients with severe cardiac adverse events, cardiac stenting, and myocardial infarction. The study stated that only omeprazole had a strong drug interaction effect on clopidogrel, while the effects of other PPIs on clopidogrel required confirmation by further studies.[4] Other studies showed that PPIs inhibited CYP2C19 activity with an inhibitory constant (Ki) of 2–6 μM for omeprazole, 8 μM for esomeprazole, 0.4–1.5 μM for lansoprazole, and 14–69 μM for pantoprazole. Therefore, pantoprazole, a weaker inhibitor of CYP2C19, may be a safer choice for patients ingesting clopidogrel.[18,19] Only 47 patients in our study used PPIs in combination with clopidogrel.

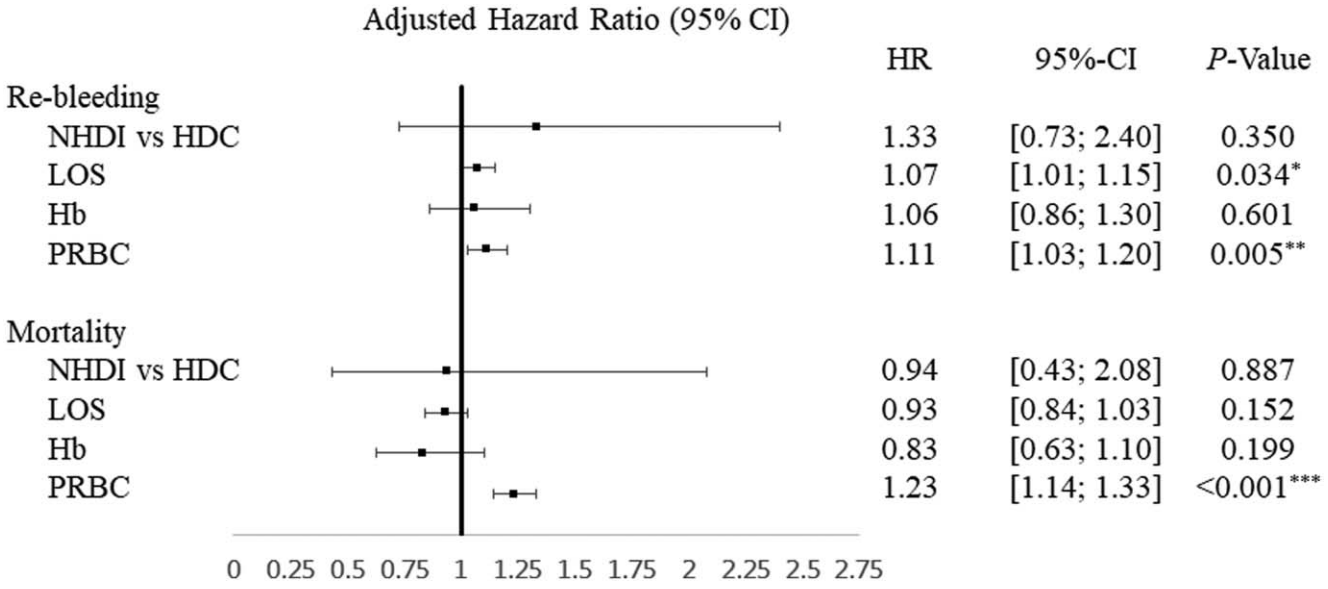

Figure 5. Secondary endpoints of multivariate regression analysis in risk of rebleeding and mortality.

Table 3

Adverse events and drug-drug interactions of PPI.

Drugs	Esomeprazole 40 mg/tab	Pantoprazole 40 mg/tab	Rabeprazole 20 mg/tab	Lansoprazole 30 mg/tab	*P* value[†]
Bone fracture event/total patients' number					
<1 year of PPI treatment	0/28	0/9	0/111	0/132	–[§]
>1 year of PPI treatment	0[‡]	0[‡]	1/13	1/10	–[§]
Cardiovascular adverse event/total patients' number					
concomitant use with clopidogrel	2/5 (40%)	0/15	0/19	2/8 (25%)	.025[*]

PPIs = proton pump inhibitors.

[†] Fisher exact test.

[‡] No patient took the medicine more than one year and no fracture occurred.

[§] Unable to calculate.

[*] $P < .05$.

The risk of CV events was relatively higher when clopidogrel was combined with esomeprazole or lansoprazole. Although our results were similar to those described in the literature, the cases of combination therapy were insufficient to draw a conclusion.

Our study found that the rebleeding risk within 7 days, LOS, and PRBC units in the HDC group were significantly higher than those in the NHDI group. As for mortality rate, PRBC units in the HDC group were significantly higher than those in the NHDI group. The NHDI regimen could reduce the risk of rebleeding within 7 days in 1 of 11 patients (NNT = 11) and reduce medication cost by US$ 400–800. Therefore, considering cost and therapeutic benefit, the NHDI regimen is not inferior to the HDC regimen, and it can achieve the same efficacy. Overall, the NHDI regimen should be considered for ease of use and low treatment cost in patients with high-risk bleeding peptic ulcers following endoscopic treatment.

5. Limitations

It is retrospective in nature. The natural characteristics of retrospective observational cohort studies may include selection bias. We will take this into consideration when designing a randomized controlled trial study in the future. Patient screening and data must be collected through electronic medical records; this is a key limitation of this study. Because of the research hypothesis, electronic medical records (including medical records, inspection, and inspection records) were complete and correct. Although incomplete records were excluded in the data collection process, the medical records contained information differences due to the different behaviors of the doctors. Another limitation of this study was that the detection rate of *H pylori* was only 57.3% (192 patients). Therefore, whether *H pylori* infection is an independent risk factor for rebleeding requires further investigation.

6. Conclusion

The results of this study revealed that the NHDI regimen showed a lower risk of rebleeding within 7 days, shorter LOS, and fewer PRBC units than that of the HDC regimen. Therefore, the NHDI PPI regimen could be considered as a recommended treatment with better outcomes and lower costs for high-risk bleeding peptic ulcer patients after endoscopic hemostasis.

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