Intravenous pantoprazole versus omeprazole for rebleeding prevention in nonvariceal bleeding after endoscopy: a retrospective cohort study

ORIGINAL ARTICLE

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ABSTRACT

OBJECTIVE

To compare the efficacy of intravenous pantoprazole and omeprazole on the reduction of the rebleeding rate in patients with nonvariceal bleeding after endoscopy.

METHODS

We conducted a retrospective cohort study comparing the rates of recurrent bleeding after successful endoscopic therapy in the patients with intravenous pantoprazole and intravenous omeprazole. Patient medical records were included if they were admitted at Khon Kaen Hospital, Thailand between January 2013 to May 2015 with the first episode of endoscopic diagnostic nonvariceal bleeding with successful hemostasis and received either intravenous pantoprazole or omeprazole immediately for recurrent bleeding prophylaxis. The primary outcome was recurrent bleeding. The secondary outcomes included surgery, blood transfusion after esophagogastroduodenoscopy (EGD) and EGD retreatment.

RESULTS

A total of 1097 medical records of the patients with nonvariceal bleeding after endoscopy were reviewed (806 in the omeprazole group and 291 in the pantoprazole group). Rebleeding occurred in 33 patients. There was no differences between the two groups in term of rebleeding rate, surgery and esophagogastroduodenoscope retreatment (adjusted odds ratio (AOR), 1.56; 95% confidence interval (CI), 0.67 to 3.61; AOR, 1.26; 95% CI, 0.36 to 4.35; AOR, 1.49; 95% CI, 0.58 to 3.81, respectively). However, we founded high-risk gastroscopic findings were the only factor associated with the higher rate of rebleeding after successful endoscopic hemostasis, surgery and EGD retreatment (AOR, 5.55; 95% CI, 2.07 to 14.93; AOR, 9.49; 95% CI, 1.79 to 50.29; AOR, 3.65; 95% CI, 1.32 to 10.08, respectively).

CONCLUSION

In patients with nonvariceal bleeding after endoscopy, using intravenous pantoprazole did not decrease the rate of rebleeding after EGD treatment than using omeprazole.

INTRODUCTION

Thailand confronts with the problem of upper gastrointestinal bleeding (UGIB) with case fatality rate ranging between 0.8 and 14%.[1] Peptic ulcer is the main cause for UGIB,[2,3,4] in which its symptom is presented a decade earlier in Asian patients comparing to the Caucasian.[5] Many studies show that after endoscopic treatment of bleeding peptic ulcer, proton pump inhibitor (PPI) can reduce the risk of rebleeding.[6,7,8] There were two previous studies comparing between intravenous pantoprazole and omeprazole; a randomized controlled trial in 2009 conducted in 90 Indian after successful endoscopic therapy of bleeding peptic ulcer, the rebleeding rate was similar among those with intravenous and oral omeprazole, pantoprazole and rabeprazole, however, it's conclusion was based on small sample size.[9] Another retrospective cohort in 2010 conducted in 807 Spanish with bleeding peptic ulcer, it found that intravenous pantoprazole was not superior to omeprazole for prevention of rebleeding. However, the application might suit the elderly as the participants were generally aged around 60 years old.[10] Hence, we conducted a retrospective cohort study in a group of Thai population with a larger sample size to overcome the limitation of the previous studies.

METHODS

STUDY DESIGN

We conducted a retrospective cohort study comparing the rate of recurrent bleeding after successful endoscopic therapy in the patient with intravenous pantoprazole and intravenous omeprazole.

PATIENT RECORDS

We verified and reviewed medical records retrospectively of all patients who admitted at Khon Kaen Hospital, Thailand between January 2013 and May 2015 with the first episode of endoscopic diagnostic nonvariceal bleeding with successful hemostasis and received intravenous pantoprazole or omeprazole immediately for recurrent bleeding prophylaxis. Successful hemostasis was established if the bleeding had stopped and formerly bleeding vessels were flattened or cavitated.[6,11,12] Patients were excluded if they were referred back to other hospitals after endoscopic, discharged by against advice before 72 hours, on anticoagulants and had multiple sources of bleeding.[13]

EXPOSURE

The use of post-endoscopic intravenous proton pump inhibitors is strongly recommended.[14] In our cohort, there were two study groups; the first group referred to the exposed group that received intravenous pantoprazole 80 mg bolus then infusion drip 8 mg/hr and another group referred to the control group that received intravenous omeprazole 40 mg twice daily.[15,16]

OUTCOME MEASURES

The primary outcome was posted successful endoscopic hemostasis rebleeding.[17] Rebleeding

was established if the ulcer was actively bleeding or if there was either coffee-grounds substance or fresh blood in the stomach.[6,9,17,18] The secondary outcomes included surgery, death, blood transfusion after esophagogastroduodenoscopy (EGD) and EGD retreatment.

DATA COLLECTION

All databases of patients diagnosed with UGIB using the International Classification of Disease (ICD) 10 who admitted in Khon Kaen Hospital. Variables including age, sex, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, hemoglobin on admission, platelet on admission, prothrombin time (PT) on admission, partial thromboplastin time (PTT) on admission, international normalized ratio (INR) on admission, coagulopathy was defined as the PT more than 13.6 sec or PTT more than 41.6 sec or INR more than 1.5,[19] underlying diseases, type of bleeding along Forrest classification, EGD report, blood transfusion after EGD, surgery records. Patients were classified as the high-risk group for recurrent bleeding if the gastroscopic finding was sporting or oozing or non-bleeding visible vessel or adherent clot or Dieulafoy's lesion.[20]

STATISTICAL ANALYSIS

All data were cleaned before the analysis. For descriptive statistics, categorical variables were summarized in term of number and percentage. For continuous variables, they were tested for their normal distributions using Kolmogorov-Smirnov test, mean and standard deviation (SD) were used if they were normally distributed while median and interquartile range (IQR) were used if they were non-normally distributed. For inferential statistics, chi-square and Fisher's exact test were used in appropriate condition for categorical variable comparison. T-test and Mann-Whitney U test were used for normally and non-normally distributed variables respectively. We used relative risk (RR) to analyze the primary outcome, post successful EGD hemostasis rebleeding, surgery, blood transfusion after EGD and EGD retreatment. For the multivariable analysis, the risk factors for the outcomes were interpreted as adjusted odds ratio (AOR) from the binary logistic regression analysis.

RESULTS

PATIENTS

Initially, 2,398 patients diagnosed with UGIB were reviewed, 1,201 were met the inclusion criteria, however, after excluding 104 patients, 1,097 were included in the analysis (Figure 1). Total of 1,097 was included in the analysis 291 were treated with pantoprazole and 806 were treated with omeprazole. Overall, mostly they were male (77.0%) with the median age of 64.1 years old (IQR 52.0 to 73.6). Their median SBP and DBP on admission were 123.0 mmHg (IQR 107.5 to 143.0) and 70.0 mmHg (IQR 60.0 to 80.0) respectively. Nearly half of them were shocked at the admission (41.9%). A quarter of all patients had coagulopathy (28.7%). For laboratory variables, their median PT, PTT, and INR on admission were 13.0 sec (IQR 12.1 to 14.4), 33.7 sec (IQR 30.0 to 39.5) and 1.09 (IQR 1.02 to 1.21), respectively. There were small numbers of patients with cardiac disease (5.0%),

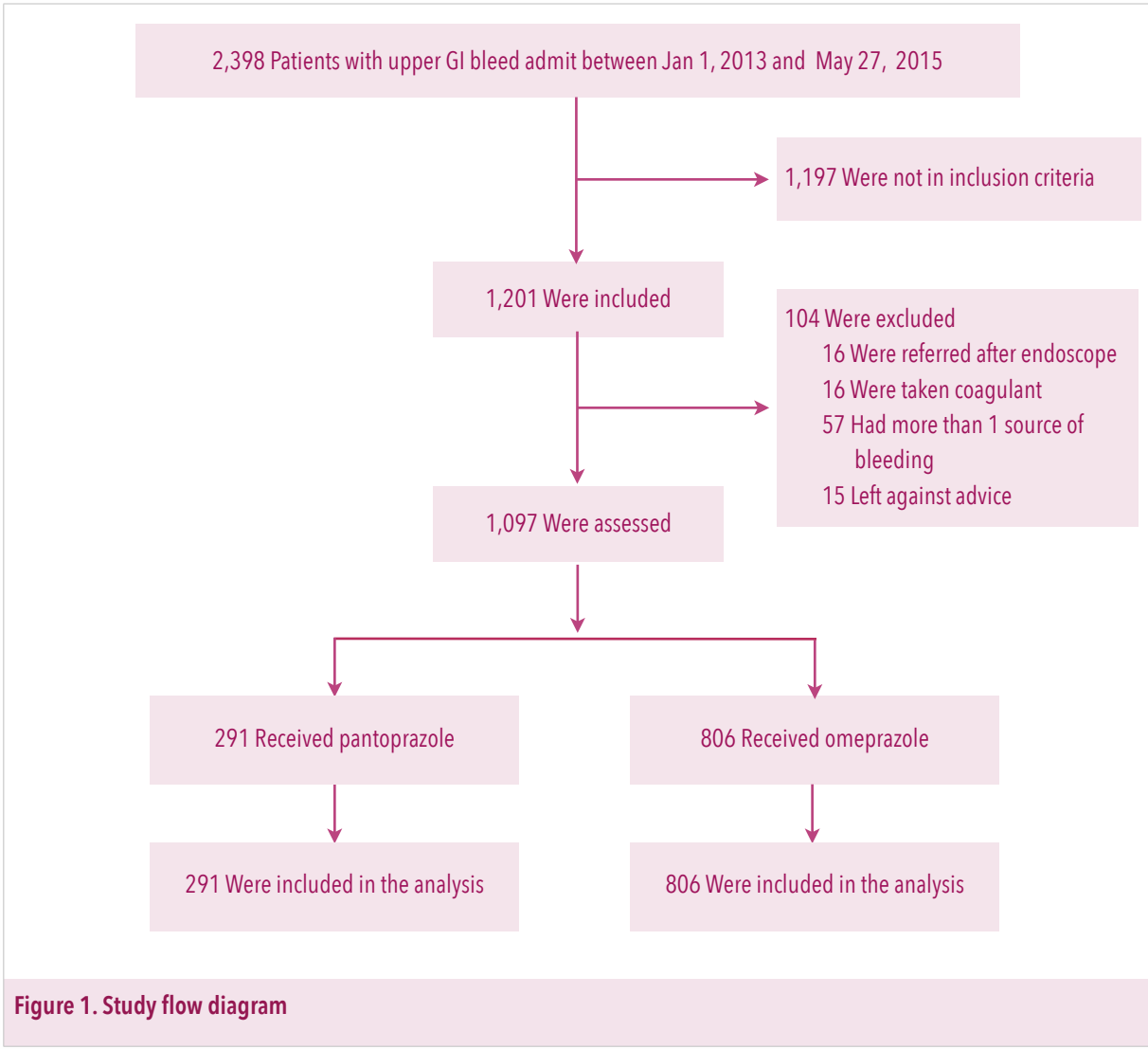

Figure 1. Study flow diagram

renal failure (10.3%) and liver disease (6.7%). For the endoscopic findings, most patients had clean-based ulcer (32.6%), gastritis (25.7%) and non bleeding visible vessel (16.4%) while there were fewer numbers of patients with spurting lesion (3.19%), oozing lesion (7.6%), adherent clot (4.6%) and flat pigmented spot (4.0%).

Comparing between the pantoprazole and the omeprazole group, the former tended to be older (P=0.01), have lower SBP (P<0.001), have lower DBP (P=0.005) and have a higher proportion of patient with shock status on the admission (P=0.03) (Table 1). For the laboratory variables, hemoglobin on admission was lower in the former group (P=0.001). For the diagnosis, patients with clean-based ulcer and gastritis were found less common in the former group (P<0.001 and P<0.001, respectively) while they had a higher

Table 1. Characteristics of the patients

Characteristic	Intravenous pantoprazole (N=291)	Intravenous omeprazole (N=806)	P Value
Age-yr			0.01
Median	65.1	63.4	
Interquartile range	55.6-75.4	50.2-73.0	
Male sex-no. (%)	225 (77.3)	620 (76.9)	0.89
Shock-no. (%)*	138 (47.4)	322 (40.0)	0.03
Systolic blood pressure-mmHg			<0.001
Median	120.0	125.0	
Interquartile range	103.0-138.0	109.0-146.0	
Diastolic blood pressure-mmHg			0.05
Median	67.0	70.0	
Interquartile range	59.0-78.0	61.0-80.0	
Heart rate-bpm			0.31
Median	92.0	90.0	
Interquartile range	80.0-104.0	78.8-102.0	
Hemoglobin-mg/dL			0.001
Median	7.0	7.7	
Interquartile range	5.3-9.1	5.9-9.9	
Platelet-10^3/uL			0.29
Median	221.0	216.0	
Interquartile range	165.0-292.0	153.0-278.3	
Prothrombin time-sec			0.34
Median	13.0	12.9	
Interquartile range	12.1-14.5	12.0-14.3	
Partial thromboplastin time-sec			0.23
Median	34.2	33.5	
Interquartile range	30.1-40.1	30.0-39.3	0.37

Table 1. Characteristics of the patients (continued)

Characteristic	Intravenous pantoprazole (N=291)	Intravenous omeprazole (N=806)	P Value
International normalized ratio			0.37
Median	55.6-75.4	50.2-73.0	
Interquartile range	225 (77.3)	620 (76.9)	
Coagulopathy-no. (%)†	138 (47.4)	322 (40.0)	0.46
Comorbidity-no. (%)			
Cardiac disease	14 (4.8)	41 (5.1)	0.85
Renal failure	32 (11.0)	81 (10.0)	0.65
Liver disease	16 (5.5)	58 (7.2)	0.32
Disseminated malignancy	3 (1.0)	15 (1.9)	0.25
Gastroscopic findings-no. (%)			
Spurting	27 (9.3)	8 (1.0)	<0.001
Oozing	57 (19.6)	26 (3.2)	<0.001
Non bleeding visible vessel	108 (37.1)	72 (8.9)	
Adherent clot	32 (11.0)	18 (2.2)	<0.001
Flat pigmented spot	8 (2.7)	36 (4.5)	0.20
Clean base	30 (10.3)	328 (40.7)	<0.001
Gastritis	14 (4.8)	268 (33.3)	<0.001
Mallory-weiss tear	1 (0.3)	8 (1.0)	0.26
Gastric mass or polyp	4 (1.4)	12 (1.5)	0.58
Dieulafoy lesion	9 (3.1)	14 (1.7)	0.17
High-risk group‡	231 (79.4)	138 (17.1)	<0.001

*Shock was defined as a systolic blood pressure less than 100 mmHg or heart rate more than 100 beats/min

†Coagulopathy was defined as the prothrombin time more than 13.6 sec or partial thromboplastin time more than 41.6 sec or INR more than 1.5

‡Patients were classified as high-risk group for recurrent bleeding if the gastroscopic finding was spurting or oozing or non bleeding visible vessel or adherent clot or Dieulafoy's lesion.

Table 2. The outcomes after endoscopic therapy

Outcome	Intravenous pantoprazole (N=291)	Intravenous omeprazole (N=806)	Relative risk (95% confidence interval)
Rebleeding in patient with first EGD reported-no. (%)	19 (6.5)	14 (1.7)	3.76 (1.91-7.40)
Spurting	6/27 (22.2)	2/8 (25.0)	0.89 (0.22-3.58)
Oozing	4/57 (7.0)	0	
Non bleeding visible vessel	7/108 (6.5)	1/72 (0.14)	4.67 (0.59-37.13)
Adherent clot	2/32 (6.3)	3/18 (16.7)	0.38 (0.07-2.04)
Clean base	0	2/328 (0.6)	
Gastritis	0	5/268 (1.9)	
Dieulafoy's lesion	0	1/14 (7.1)	
High-risk lesion	19/231 (8.2)	7/138 (5.1)	1.62 (0.70-3.76)
EGD retreatment-no. (%)*	14 (4.8)	13 (1.6)	2.98 (1.42-6.27)
Surgery-no. (%)	8 (2.7)	6 (0.7)	3.69 (1.29-10.55)
Blood transfusion after endoscope-unit			<0.001
Mean	0.9	0.3	
Median	0	0	
Interquartile range	0.0-1.0	0.0-0.0	
Death	3(1.0)	5(0.6)	1.66 (0.4-6.91)

EGD=esophagastroduodenoscope.
*High risk was defined as the EGD finding was spurting, oozing, non bleeding visible vessel, adherent clot or Dieulafoy's lesion.Patient with rebleeding was retreated by EGD. If EGD could not stop bleeding, the patient would had controlled bleeding by surgery. Some patients was passed re EGD and shifted to surgery.[21,22]

proportion of patient with spurting, oozing, adherent clot and non bleeding visible vessel (P<0.001, P<0.001, P<0.001 and P<0.001, respectively).

However, proportion of male patients, median of heart rate, level of platelet, PT, PTT, INR, proportion of patient with coagulopathy, comorbidity including cardiac disease, renal failure, liver disease, disseminated malignancy, gastroscopic findings consisting of black spot, Mallory-Weiss tear, gastric cancer, Dieulafoy's lesion were similar between the two groups.

OUTCOMES

From the Table 2, the rebleeding rate was higher in the pantoprazole group (6.5%) than in the omeprazole group (1.7%) (RR, 3.76; 95% CI, 1.91 to 7.40). Similarly, endoscopic retreatment rate was higher in the pantoprazole group (4.8%) than in the omeprazole group (1.6%) (RR, 2.98; 95% CI,

Table 3. Risk factors associated with the outcomes

Factors	Rebleeding	Surgery	EGD retreatment
	Odds ratio (95% confidence interval)		
Age-yr	1.01 (0.99-1.02)	0.97 (0.93-1.01)	1.01 (1.00-1.02)
Male sex	2.94 (0.82-10.49)	1.43 (0.29-7.07)	3.87 (0.79-18.98)
Intervention Pantoprazole	1.56 (0.67-3.61)	1.26 (0.36-4.35)	1.49 (0.58-3.81)
Shock	1.43 (0.69-2.96)	0.82 (0.26-2.60)	2.13 (0.94-4.85)
Hemoglobin-mg/dL	1.02 (0.89-1.17)	0.86 (0.68-1.08)	1.06 (0.91-1.22)
Platelet 10^3/uL	1.00 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)
Coagulopathy	1.95 (0.90-4.21)	3.82 (1.11-13.20)	1.81 (0.77-4.26)
High-risk EGD findings	5.55 (2.07-14.93)	9.49 (1.79-50.29)	3.65 (1.32-10.08)
Comorbidity			
Cardiac disease	1.22 (0.25-5.89)	4.41 (0.84-23.31)	1.41 (0.28-7.07)
Renal failure	0.27 (0.04-2.10)		0.36 (0.05-2.78)
Liver disease	0.43 (0.05-3.34)		0.43 (0.05-3.38)
Disseminated malignancy	2.83 (0.30-26.92)		4.08 (0.43-38.59)

EGD=esophagogastroduodenoscopy

1.42 to 6.27). However, receiving a blood transfusion after endoscope was lower in the pantoprazole group than in the omeprazole group (P<0.001 by Mann-Whitney U test). There were no differences between the two study groups in rebleeding rate in those with spurting ulcer, nonbleeding visible vessel ulcer, adherent clot ulcer, high-risk lesion and receiving surgical treatment. For the omeprazole group, there was no rebleeding in those with oozing ulcer, while in the pantoprazole group, there was no rebleeding in the clean-based ulcer, gastritis and dieulafoy's lesion.

FACTORS ASSOCIATED WITH THE OUTCOMES

From the logistic regression analysis, pantoprazole was not associated with lower rate of rebleeding after successful endoscopic hemostasis, surgery and re endoscopy (AOR, 1.56; 95% CI, 0.67 to 3.61; AOR, 1.26; 95% CI, 0.36 to 4.35; AOR, 1.49; 95% CI, 0.58 to 3.81, respectively). However, coagulopathy factor was associated with surgery (AOR, 3.82; 95% CI, 1.11 to 13.20), while high risk gastroscopic findings were the only factors associated with whole of three outcomes such as higher rate of rebleeding after successful endoscopic hemostasis, surgery and re endoscopy

(AOR, 5.55; 95% CI, 2.07 to 14.93; AOR, 9.49; 95% CI, 1.79 to 50.29; AOR, 3.65; 95% CI, 1.32 to 10.08, respectively) (Table 3).

However, median of age, proportion of male patients, proportion of patient with shock status, level of hemoglobin, level of platelet, comorbidity include cardiac disease, renal failure, liver disease, disseminated malignancy were found not associated with rebleed, surgery, and EGD retreatment, while coagulopathy was found not associated with rebleeding and EGD retreatment.

DISCUSSION

MAJOR FINDINGS

In our study, we found that pantoprazole was not associated with a lower rate of rebleeding in the patients with nonvariceal bleeding after successful endoscopic hemostasis. However, coagulopathy factor was associated with surgery, while high-risk gastroscopic findings were the only factors associated with the whole of three outcomes such as higher rate of rebleeding after successful endoscopic hemostasis, surgery and re endoscopy.

STRENGTHS AND LIMITATIONS OF THE STUDY

The sample size which could present the different outcomes between the pantoprazole and the omeprazole group was 1,184 patients but the sample size of this study was 1,097 patient. In this study, the information of patients was presented with many characteristics. The confounders were indicated and used in the analysis.

However, there were limitations to this study. The patients in this study were excluded by the condition with more than one possible source of bleeding. Thus the patients with more than one cause of upper gastrointestinal bleeding were not suitable for using our outcome to treatment in them. In addition, the EGD technique and experience of practitioner were effects to the rate of rebleeding.[12] In Khon Kaen Hospital, there were many patients were treated by residents. Thus the result of treatment in this hospital may be out of standard in some patients with the emergency condition.

COMPARISON WITH OTHER STUDIES

In the previous study, their findings shown that there was no difference between intravenous pantoprazole and omeprazole similarly to ours.[9] In the other hand, the previous study focused in pH to be their primary outcome and found only the hemostatic instability to be risk rebleeding without mentioning the pantoprazole and omeprazole effects to rebleeding directly.[9] While in the present study, we focused on rebleeding and the gastroscopic findings is the only one risk factor of rebleeding.

In addition, the most common cause of our study and other studies were the clean-based ulcer[2,3,23] whereas the older studies suggested that peptic ulcer disease was responsible for approximately half of the upper gastrointestinal bleeding,[4] more recent studies suggest it is now the less common cause.[2,3,24] In 2011, there was a randomized controlled trial comparing the efficacy of oral omeprazole versus intravenous pantoprazole in 106 in Iranian, their findings suggested the similar efficacies of the oral

omeprazole and intravenous pantoprazole on prevention of rebleeding after endoscopic therapy in patients with high risk bleeding peptic ulcers.[25] However, in the present study, we also found the similar efficacies of the intravenous pantoprazole and the intravenous omeprazole on prevention of rebleeding in nonvariceal bleeding with successful hemostasis.

CONCLUSION AND IMPLICATION

Intravenous pantoprazole and intravenous omeprazole had no difference in relation to prevention of rebleeding in the patient with nonvariceal bleeding after endoscopy. Thus, using whether pantoprazole or omeprazole depends on the clinical practice guideline, cost-effectiveness in each settings as well as the patient preference.

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