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Effect of pantoprazole on prevention of gastrointestinal bleeding in acute coronary syndrome patients with high risk of gastrointestinal bleeding

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ABSTRACT

Background and Objective: Determination of best preventive approach for gastrointestinal bleeding in Acute Coronary Syndrome (ACS) patients with high risk of gastrointestinal bleeding is crucial. This study aimed to determine the effect of pantoprazole on prevention of gastrointestinal bleeding in ACS patients with high risk of gastrointestinal bleeding.

Methods: This randomized clinical trial was performed in emergency department of Imam Hussein Hospital in Tehran, Iran between 2018 and 2019 among 1276 consecutive ACS patients with high risk of gastrointestinal bleeding.The participants were randomly received either pantoprazole 40 mg or famotidine 40 mg daily. The melena, hematemesis, hematochezia, and hemoglobin level were compared across the groups after one month.

Findings: The results in this study demonstrated that melena was seen in 1.1% and 3.8% in pantoprazole and famotidine groups, respectively with significant difference (P=0.002). Hematemesis was seen in 0.6% and 1.9% in pantoprazole and famotidine groups, respectively with significant difference (P=0.044). Also, hematochezia was seen in 0.3% and 0.8% in pantoprazole and famotidine groups, respectively without significant difference (P=0.452). The mean hemoglobin was 11.98 and 11.82 in pantoprazole and famotidine groups, respectively with significant difference (P=0.021).

Conclusion: This study showed that pantoprazole (versus famotidine) is effective for prevention of gastrointestinal bleeding in Acute Coronary Syndrome patients with high risk of gastrointestinal bleeding.

Keywords: Pantoprazole, Gastrointestinal bleeding, Acute coronary syndrome

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Introduction

Acute coronary syndrome (ACS) is presentation of various symptoms of myocardial ischemia includes unstable angina, non-ST elevation of myocardial ischemia, and ST elevation of myocardial ischemia (1). Despite significant decrease in mortality rate in ACS patients, the five-year fatality rate is nearly forty percent (2). Combination therapy with aspirin and clopidogrel is good standard preventive approach to decrease the rate of recurrence and mortality (3). Anti-thrombotic and anti-platelet medications can result in increased gastrointestinal bleeding (GIB) (4, 5). Upper GIB is seen among 4% of cardiovascular patients receiving aspirin and clopidogrel in six-month follow-up especially among patients under treatment with anti-platelet and anti-thrombolytic medications (6).

Proton pump inhibitors (PPI) can inhibit the ATPhosphatase-KH enzyme in gastric mucosa and are used to prevent such hemorrhages (4). Mortality risk is increased in patients receiving clopidogrel plus PPI and the possible etiology is that PPI may affect platelet aggregation by cytochrome system. But there are few studies about high risk of GIB in patients with cardiovascular diseases. Also, the studies are usually focused on clopidogrel, aspirin, and PPI that may affect the true interaction between clopidogrel and PPI (4). Pantoprazole is an irreversible PPI that can reduce gastric acid secretion with 40 mg administration. It has been better than ranitidine and omeprazole for treatment of peptic ulcer disease and reflex diarrhea (7-13). Hence in this study the main aim was to determine the effect of pantoprazole on prevention of GIB in ACS patients with high risk of gastrointestinal bleeding.

Methods

This double-blind randomized clinical trial was performed in Emergency Department of Imam Hussein Hospital in Tehran, Iran between 2018 and 2019. Totally, 1276 consecutive ACS patients with high risk of GIB were enrolled. Inclusion criteria were one or more risk factors among these ones; age older than 75 years, peptic ulcer disease history, GIB history, renal failure history (creatinine over 2 mg/dl), and cardiogenic shock. The exclusion criteria were pregnancy, hepatic failure, and history of pantoprazole hypersensitivity, severe GIB, and dissatisfaction in subjects. The data were gathered by checklist, interview, and observation.

Study was approved by ethical committee of Shahid Beheshti University of Medical Sciences (NO: 1397316) and Helsinki Declaration was respected across the study. Also, informed consent was received from all patients. The subjects were randomly assigned with block randomization of two subjects to receive either pantoprazole 40 mg or famotidine 40 mg daily. The melena, hematemesis, hematochezia, and hemoglobin level were compared across the groups in one month by phone call and visit in a weekly manner. The drug offering was done by blinded subjects. Data analysis was done by SPSS version 25.0 among 1276 patients in two groups of 638 subjects. The utilized tests were Independent-Sample-T, Chi-Square, and Exact-Fisher and the P values under 0.05 were considered statistically significant.

Results

Ninteen percent of participants in pantoprazole group and 20.5% in famotidine group were older than 75 years of old, showing a non-significant difference (P=0.428). Totally 58.8% and 58.3% in pantoprazole and famotidine groups were male, respectively (P=0.955). Background disease history was same across the groups (Table 1). As shown in Table 2, melena was seen in 1.1% and 3.8% in pantoprazole and famotidine groups, respectively with significant difference (P=0.002). Hematemesis was seen in 0.6% and 1.9% in pantoprazole and famotidine groups, respectively with significant

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difference (P=0.044). Moreover, hematochezia was seen in 0.3% and 0.8% in pantoprazole and famotidine groups, respectively without significant difference (P=0.452). The mean hemoglobin was 11.98 and 11.82 in pantoprazole and famotidine groups, respectively with significant difference (P=0.021).

As shown in Table 3, the melena was differed by age in pantoprazole (P=0.027) and famotidine (P=0.001) groups. As demonstrated in Table 4, the hematemesis was differed by age not in pantoprazole (P=0.061) but in famotidine (P=0.001) groups. As shown in Table 5, the hematemesis was differed by age not in pantoprazole (P=0.165) but in famotidine (P=0.036) groups. Also, the history of background diseases was related to further risk of the melena, hematemesis, and hematocezia including CRF, PUD, GIB (only for melena), CHF, and NSAID use (P < 0.05).

Table 1. Background disease history across the groups

Variable	Pantoprazole	Famotidine	P Value
CRF History	27 (4.2%)	20 (3.1%)	0.298
PUD History	33 (5.2%)	22 (3.4%)	0.129
GIB History	32 (5.0%)	20 (3.1%)	0.089
CHF History	27 (4.2%)	17 (2.7%)	0.125
NSAID Use	49 (7.7%)	34 (5.3%)	0.089

Table 2. GIB rate across the groups

Variable	Pantoprazole	Famotidine	P Value
Melena	7 (1.1%)	24 (3.8%)	0.002
Hematemesis	4 (0.6%)	12 (1.9%)	0.044
Hematochezia	2 (0.3%)	5 (0.8%)	0.452

Table 3. Melena rate by age in groups

Group				Melena		Total
				Pos	Neg	
Pantoprazole	**Age**	<75	Count	3	514	517
			% within Age	6%	99.4%	100.0%
		>75	Count	4	117	121
			% within Age	3.3%	96.7%	100.0%
	Total		Count	7	631	638
			% within Age	1.1%	98.9%	100.0%
Famotidine	**Agee**	<75	Count	8	499	507
			% within Age	1.6%	98.4%	100.0%
		>75	Count	16	115	131
			% within Age	12.2%	87.8%	100.0%
	Total		Count	24	614	638
			% within Age	3.8%	96.2%	100.0%

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Table 4. Hematemesis rate by age in groups

Group				Hematemesis		Total
				Pos	Neg	
Pantoprazole	Age	<75	Count	2	515	517
			% within Age	.4%	99.6%	100.0%
		>75	Count	2	119	121
			% within Age	1.7%	98.3%	100.0%
	Total		Count	4	634	638
			% within Age	.6%	99.4%	100.0%
Famotidine	Agee	<75	Count	4	503	507
			% within Age	.8%	99.2%	100.0%
		>75	Count	8	123	131
			% within Age	6.1%	93.9%	100.0%
	Total		Count	12	626	638
			% within Age	1.9%	98.1%	100.0%

Table 5. Hematochezia rate by age in groups

Group				Hematochezia		Total
				Pos	Neg	
Pantoprazole	Age	<75	Count	0	517	517
			% within Age	.0%	100.0%	100.0%
		>75	Count	2	119	121
			% within Age	1.7%	98.3%	100.0%
	Total		Count	2	636	638
			% within Age	.3%	99.7%	100.0%
Famotidine	Agee	<75	Count	2	505	507
			% within Age	.4%	99.6%	100.0%
		>75	Count	3	128	131
			% within Age	2.3%	97.7%	100.0%
	Total		Count	5	633	638
			% within Age	.8%	99.2%	100.0%

Discussion

Our findings indicated that the pantoprazole versus famotidine had higher efficacy for reduction in risk of GIB in patients with ACS. In a study among 665 ACS cases, 3.6% and 1.2% had GIB in placebo and pantoprazole groups, respectively. Major bleeding was more common in placebo group. The mortality rate was 10.2% and 10.5% in placebo and pantoprazole groups, respectively in their study. In our study there was no placebo group but the results were better in pantoprazole versus famotidine group. Jensen et al. (7) reported that dual anti-platelet therapy can reduce the risk of ischemic events after ACS but upper GIB may be increased. In their study the screening for risk factors of UGIB and later treatment with PPI could not reduce the risk of UGIB. The use of PPI had higher accommodation with anti-platelet therapy. Consistent with these findings, the pantoprazole showed relatively good efficacy in our study.

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Cardoso et al. (8) compared clopidogrel use with and without PPI administration in a meta-analysis and found that PPI plus clopidogrel use resulted in decreased risk of GIB. In their study, simultaneous use of PPI and clopidogrel was accompanied with lower GIB. Schreiner et al. (9) assessed efficacy of PPI for reduction of GIB among 781 out of 4162 patients. They found low rate of use of PPI after ACS and recommended the use of this medication especially in patients with multiple risk factors. Barada et al. (10) reported that 69% of cases used PPI during hospital stay. UGIB was seen in 0.7% that was major type in 0.2%. The bleeding rate was same across those with and without PPI use. Reversely, they reported that risk of UGIB is low in ACS cases and use of PPI is not recommended. Yasuda et al. (11) reported in patients with ACS that use of PPI versus H2 blocker had higher stenotic lesions in coronary arteries. They showed lower anti-platelet effect in subjects that used PPI.

Mo et al. (12) showed that PPI are effective for prevention of UGIB related to LDA and simultaneous use of PPI and clopidogrel cannot increase the rate of major adverse cardiac events. It was also related to decreased risk of UGIB in patients using PPI versus H2-blocker. Tsai et al. (13) reported that clopidogrel plus PPI could decrease the rate of GIB. But it was accompanied with increased risk of stroke. In their study subjects were those using clopidogrel alone, clopidogrel plus PPI, and users of aspirin plus PPI. Two first groups had lower risk of GI bleeding versus third group. This study showed that pantoprazole (versus famotidine) is effective for prevention of gastrointestinal bleeding in ACS patients with high risk of gastrointestinal bleeding. However further studies are required to attain more definite results and development of the best strategies to reduce stroke and ischemia risk as well as the risk of GI bleeding in ACS patients.

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Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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