Logistic regression analysis of risk factors for upper gastrointestinal bleeding induced by PCI in combination with double antiplatelet therapy for STEMI patients

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Abstract

Objective **: To analyze the risk factors for upper gastrointestinal bleeding (UGIB) in patients with ST-segment elevation myocardial infarction (STEMI) during double antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI).**

Methods **: A total of 388 patients treated from January 2015 to September 2017 due to STEMI were selected. Thirty-two cases of UGIB occurring during DAPT after PCI were included as a UGIB group, and another 356 cases without UGIB were set as a control group. Age, gender, body mass index, smoking, drinking, history of previous diseases (hypertension, diabetes and digestive tract diseases), infection of Helicobacter pylori (Hp), combined use of other drugs (statins, NSAIDs, β receptor blockers, PPI, H_2RA and dabigatran etexilate), as well as serum levels of creatinine (Cr), alanine transaminase (ALT) and C-reactive protein (CRP) were compared. The risk factors for UGIB were subjected to univariate and logistic regression analyses.**

Results **: Compared with the control group, the UGIB group had significantly longer hospital stay, and higher proportion of discontinuation of antithrombotic drugs and mortality rate ($P<0.05$). Logistic regression analysis showed that age ($P=0.002$), smoking ($P=0.000$), Hp infection ($P=0.020$), history of digestive tract diseases ($P=0.030$) and renal insufficiency ($P=0.041$) were independent risk factors for UGIB, and use of PPI ($P=0.028$) was a protective factor for UGIB.**

Conclusions **: Old age, smoking, Hp infection, history of digestive tract diseases and renal insufficiency are risk factors for UGIB caused by PCI combined with DAPT in patients with STEMI. Proper use of PPI thereafter can reduce the incidence rate of UGIB.** (Acta gastroenterol. belg., **2020**, 83, **245-248**).

Keywords : myocardial infarction, percutaneous coronary intervention, upper gastrointestinal bleeding, risk factor.

Introduction

As a common clinical cardiovascular disease, coronary heart disease has an annually increasing incidence rate. ST-segment elevation myocardial infarction (STEMI), as the most critical type, features acute onset, poor prognosis and high mortality rate, posing a serious threat to the quality of life (1). Percutaneous coronary intervention (PCI) is one of the main methods for treating STEMI in clinical practice, which allows reperfusion of occlusive vessels and greatly reduces the immediate mortality rate of STEMI patients (2). Platelets play key roles in myocardial perfusion injury and increase of ischemic areas in STEMI patients. The reperfusion injury of patients is evidently aggravated, so it is necessary to supplement antiplatelet drugs in the perioperative period of PCI and long-term treatment after surgery. Double antiplatelet therapy (DAPT) using aspirin in combination with clopidogrel is the standard medication after PCI, with improved benefits after over 1 year of oral administration (3). However, DAPT markedly elevates the risk of bleeding, especially upper gastrointestinal bleeding (UGIB). The best timing for treatment may have been missed because of hidden symptoms, leading to serious consequences and obviously affecting the prognosis of patients (4). Thereby motivated, we herein analyzed the risk factors for UGIB induced by DAPT after PCI in patients with STEMI, aiming to provide valuable evidence for prevention and treatment.

Methods

Subjects

A total of 388 patients who were treated in our hospital from January 2015 to September 2017 due to STEMI were retrospectively studied. Thirty-two cases of UGIB occurring during DAPT after PCI were included as a UGIB group, and another 356 cases without UGIB were set as a control group. Each patient was orally administered with 300 mg aspirin (Bayer Health Care, Germany) and 600 mg clopidogrel (Hangzhou Sanofi Pharmaceutical Co., Ltd., China) before surgery. On the postoperative 2nd day, the patient was orally given 100 mg aspirin and 75 mg clopidogrel once a day as a maintenance dose. Subsequently, the patients were treated for one year based on bleeding symptoms, and followed up. UGIB was diagnosed by endoscopy in the case of brown liquid vomit, black stool, hematochezia or positive result of fecal occult blood. Inclusion criteria : 1) Patients in accordance with the diagnostic criteria of STEMI (two of the following three requirements must be met) : with persistent chest pain for ≥30 min ; electrocardiogram showed ST-segment elevation of above 0.2 mV in two consecutive leads accompanied by

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Submission date : 01/10/2019
Acceptance date : 11/01/2020

dynamic changes ; with positive results of troponin test ; 2) within 12 h after STEMI onset ; 3) 100% occlusion of coronary arteries determined by coronary angiography ; 4) without contraindications for antiplatelet therapy or PCI ; 5) without serious digestive system diseases within 1 year ; 6) with complete clinical data. Exclusion criteria : 1) Complication with severe liver and kidney insufficiencies ; 2) with immune system diseases ; 3) patients during pregnancy or lactation ; 4) with severe heart failure ; 5) with malignant tumors. This study has been approved by the ethics committee of our hospital, and written informed consent has been obtained from all patients

Methods

The baseline clinical data of patients were collected, including age, gender, body mass index (BMI), smoking, drinking, history of hypertension, diabetes or digestive tract diseases, infection of *Helicobacter pylori* (Hp), combined use of other drugs (statins, non-steroidal anti-inflammatory drugs (NSAIDs), beta blockers, proton pump inhibitors (PPI), H_2 receptor antagonists (H_2RA) and dabigatran etexilate), as well as serum levels of creatinine (Cr), alanine transaminase (ALT) and C-reactive protein (CRP).

Statistical analysis

All data were analyzed by SPSS20.0 software. The normally distributed categorical data were represented as mean ± standard deviation, and intergroup comparisons were performed by the independent t test. The numerical data were expressed as percentage, and intergroup comparisons were conducted with the Chi-square test or Fisher's exact test. The risk factors for UGIB were subjected to logistic regression analysis, and OR and 95%CI values were calculated. P<0.05 was considered statistically significant.

Results

Clinical characteristics and outcomes

There were no significant differences in the surgical time, number of infarct-related vessels and proportion of intraoperative thrombus removal between the two groups (P>0.05). Compared with the control group, the UGIB group had significantly longer hospital stay, and higher proportion of discontinuation of antithrombotic drugs and mortality rate (P<0.05) (Table 1).

Univariate analysis of risk factors for UGIB

Univariate analysis showed that the age, smoking, Hp infection, history of hypertension, history of digestive tract diseases, use of dabigatran etexilate, PPT or H_2RA, as well as serum Cr and CRP levels of the two groups were significantly different (P<0.05). However, there were no significant differences between gender, drinking history, history of diabetes, use of statins, NSAIDs or β receptor blockers and ALT level (P>0.05) (Table 2).

Multivariate logistic regression analysis of risk factors for UGIB

Multivariate logistic regression analysis showed that age (OR=267.31, P=0.002), smoking (OR=341.45, P=0.000), Hp infection (OR= 22.19, P=0.020), history of digestive tract diseases (OR=20.82, P=0.030) and renal insufficiency (OR=256.12, P=0.041) were independent risk factors for UGIB, and use of PPI (OR=156.75, P = 0.028) was a protective factor for UGIB (Table 3).

Discussion

STEMI is caused by severe ischemia of the myocardium in patients with coronary artery disease in a short period of time due to sharp decrease of coronary blood supply. With the improvement of living standards and lifestyle changes in China, the incidence rate of this disease has increased annually, with nearly 2 million new cases reported (5). Emergency PCI can open the blood vessels of STEMI infarction and quickly restore blood flow, which is one of the most effective ways to prevent disease aggravation. As a commonly used drug for DAPT after PCI, aspirin can inhibit the production of thromboxane A2 by blocking cyclooxygenase-1, and clopidogrel is an ADP receptor inhibitor that blocks P2Y12 receptor after activation by the liver (6). Aspirin inhibits platelet aggregation and affects the protective

Table 1. — **Clinical characteristics and outcomes**

Item	UGIB group (n=32)	Control (n=356)	P value
Surgical time (min)	43.21±11.71	44.72±13.63	0.544
Number of infarct-related vessels [n(%)]			
Left anterior descending branch	16 (50.00%)	185 (51.97%)	0.831
Right coronary artery	13 (40.63%)	143 (40.17%)	0.96
Left circumflex branch	3 (9.38%)	28 (7.87%)	0.763
Use of intraoperative thrombus removal [n(%)]	23 (71.88%)	252 (70.79%)	0.897
Hospital stay (d)	6.23±2.12	5.19±1.87	0.002
Proportion of discontinuation of antithrombotic drugs [n(%)]	8 (25.00%)	32 (8.99%)	0.004
Morality rate [n(%)]	2 (6.25%)	4 (1.12%)	0.024

Table 2. — **Baseline clinical data**

Characteristic	UGIB group (n=32)	Control (n=356)	P value
Age	67.23±6.43	53.74±3.26	<0.01
Male	23 (71.88%)	98 (69.94%)	0.819
BMI	26.32±1.25	25.95±1.06	0.063
Smoking	17 (53.13%)	98 (27.53%)	0.002
Drinking	4 (12.50%)	23 (6.46%)	0.198
Hp infection	9 (28.13%)	44 (12.36%)	0.013
History of previous diseases			
Hypertension	21 (65.63%)	200 (56.18%)	0.301
Diabetes	14 (43.75%)	156 (43.82%)	0.994
Digestive tract diseases	11 (34.38%)	43 (12.08%)	<0.01
Drug combination			
Statins	12 (37.50%)	114 (32.02%)	0.526
NSAIDs	9 (28.13%)	100 (28.09%)	0.997
β receptor blockers	16 (50.00%)	183 (51.40%)	0.879
PPI	8 (25.00%)	168 (47.19%)	0.016
H_2RA	9 (28.13%)	172 (48.31%)	0.028
Dabigatran etexilate	6 (18.75%)	50 (14.04%)	0.468
ALT (U/L)	362.78±48.35	353.12±36.78	0.167
Cr (mmol/L)	148.32±31.56	92.15±23.62	<0.01
CRP (mg/L)	26.23±4.32	25.12±3.28	0.038

Table 3. — **Multivariate logistic regression analysis of risk factors for UGIB**

Factor	B	SE	Wald	P value	OR value	95%CI
Age	0.547	0.276	12.685	0.002	7.312	1.179~11.436
Smoking	0.632	0.317	13.474	<0.01	4.456	1.128~6.512
Hp infection	0.562	0.378	13.874	0.020	2.197	1.028~21.589
Hypertension	0.716	0.533	13.888	0.236	4.5835	0.202~2.521
History of digestive tract diseases	0.623	0.312	13.238	0.030	20.821	1.362~12.423
PPI	-0.756	0.176	12.323	0.028	0.575	0.318~0.653
H_2RA	0.328	0.658	13.239	0.089	8.754	0.365~12.723
Cr	0.456	0.712	11.293	0.041	6.122	1.128~16.845
CRP	0.757	0.471	14.751	0.115	5.558	0.451~6.874

effect of PGI2 on the gastric mucosa. Even if enteric-coated capsules do not directly stimulate the stomach, they still affect the gastric mucosa during drug absorption (7). In a previous study, clopidogrel increased the probability of bleeding while combating platelet aggregation, but the mechanism of action was not elucidated (8). As a prodrug, dabigatran etexilate releases active substances by esterase hydrolysis after oral administration to exert anticoagulant effect, which can enhance the efficacy of DAPT. However, dabigatran etexilate increases the risk of UGIB. In this study, dabigatran etexilate was not an independent risk factor for UGIB. The combination of NSAIDs or H2RA is also a risk factor for UGIB in patients with STEMI receiving DAPT after PCI, which, however, was not found herein, probably due to the small sample size that cannot reflect the actual situation (9). It is thus necessary to conduct large-scale clinical studies.

The incidence rate of UGIB in elderly patients significantly increases, probably because the gastric mucosal function declines with aging and blood supply to the gastric mucosa is insufficient for repair, accompanied by the weakening of organ function. The slower metabolism of drug leads to an increase in plasma concentration, which may be mainly responsible for UGIB in elderly patients (10). Serum Cr level is an independent risk factor for UGIB, suggesting that the ability of metabolizing drugs is greatly weakened owing to renal insufficiency and gastric mucosal damage is thus aggravated (11). Whether smoking is a risk factor for UGIB is still controversial. In this study, smoking was a risk factor for UGIB. The gastric parietal cells of smoking patients are more prone to hyperplasia and stimulation. The secreted gastric acid then inhibits the synthesis of prostaglandins in the gastroduodenal mucosa, reduces the blood flow of the gastric mucosa, and ultimately impairs the protective barrier of the digestive tract (12). In addition, the activity of NO synthase in the blood is inhibited by inhalation of smoke, and the synthesis of epidermal growth factor in gastric mucosa is hindered, which is not conducive to the healing of lesions such as ulcers (13). This study revealed that the combination of PPI-based acid suppressant reduced the incidence rate of UGIB, whereas the risk of UGIB in patients without PPI significantly increased. Gastric ulcer and gastritis

are more common in patients with UGIB which can be prevented by taking gastric mucosal protective agents. Although UGIB can also prevented and protected by H2RA, its efficacy is inferior to that of PPI.

The onset and progression of coronary heart disease have been related to Hp infection (14). Therefore, the relationship of Hp infection with UGIB after DAPT was herein analyzed. Hp infection is an independent risk factor for UGIB. Hp can express mediators that disrupt the barrier function of the gastric mucosa, such as proteases and phospholipase A. These media also impede the absorption of gastric and exogenous nutrients to affect gastric function. It can also synergize with antiplatelet drugs to aggravate digestive tract damage (15). Hp infection can cause inflammation. Due to the massive secretion of inflammatory mediators and acute reactants, the physiological function of gastric mucosal cells can be destroyed, which results in damage to the gastric mucosa, mainly manifested as UGIB. In this study, the UGIB group had significantly higher CRP level than that of the control group. As a marker of inflammatory response, CRP plays an important role in predicting infection and cardiovascular disease, which may be responsible for the increase in Hp infection and CRP level of the UGIB group (16). Moreover, the history of digestive system disease was also an independent risk factor for UGIB, which indirectly proved that Hp caused UGIB after DAPT.

Compared with the control group, the hospitalization time of the UGIB group was significantly prolonged, and the proportion of drug withdrawal and mortality were significantly increased. Hence, the incidence rate of ischemic events rose after drug discontinuation, which seriously affected the prognosis of patients. If the drug is not discontinued, UGIB is aggravated. If the case of considerable bleeding, blood transfusion is needed, so patients with ischemic heart disease and anemia easily undergo vascular contract and platelet aggregation, also exacerbating the disease and affecting the prognosis (17).

In summary, emergency PCI combined with DAPT can cause UGIB in STEMI patients due to a variety of factors. During treatment, particular attention should be paid to the risk of bleeding, age, history of smoking, Hp infection, history of digestive tract diseases and renal function. Using PPI during DAPT is beneficial to reducing the occurrence of UGIB. In general, patients' condition should be fully evaluated and a reasonable treatment plan should be proposed to decrease complications as much as possible and to improve the prognosis. Nevertheless, this study still has limitation. This is a single-center retrospective study, and the size of included samples is small, giving some different results from those of previous literatures. In the future, we will perform multi-center studies and increase the sample size.

Conflict of interest

None to declare

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