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Original Article

Efficacy of bivalirudin sequential dose therapy in patients with ST-segment elevation myocardial infarction undergoing emergency intervention during the perioperative period

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Abstract: Objective: This study aimed to observe the efficacy and safety of bivalirudin sequential dose therapy in patients with ST-segment elevation myocardial infarction (STEMI) undergoing emergency percutaneous coronary intervention (PCI). Methods: A total of 86 patients that were diagnosed with STEMI and underwent emergency PCI, from January 2012 to March 2017, were retrospectively analyzed. Main observational indexes included in-stent thrombosis rate and incidence of various bleeding events within 30 days postoperatively. Other observational indexes included incidence of major adverse cardiac and cerebrovascular events (MACCE) and thrombocytopenia within 30 days. Results: Enrolled patients had an average age of 62.56±12.97 years old. The percentage of males was 82.6% and percentage of PCI was 97.7%. During the 30 days of follow-up, no patients had in-stent thrombosis. Incidence of total bleeding events, MACCE, and postoperative thrombocytopenia were 3.49%, 2.26%, and 2.26%, respectively. Conclusion: Bivalirudin sequential dose therapy can be safely and effectively applied in patients with STEMI undergoing emergency PCI. This therapy can effectively control perioperative risk of bleeding during emergency PCI, with good anticoagulant effects.

Keywords: Bivalirudin, acute myocardial infarction, percutaneous coronary intervention, thromboembolism, tirofiban

Introduction

Bivalirudin is a novel type of direct thrombin inhibitor, characterized by strong antithrombotic effects, short half-life, and ability to minimize thrombocytopenia [1]. Since its approval by the US Food and Drug Administration (FDA) in 2010, application of bivalirudin in percutaneous coronary intervention (PCI) has attracted the attention of medical scholars. Several studies have demonstrated that bivalirudin can significantly reduce the risk of bleeding, compared to heparin and platelet glycoprotein IIb/IIIa receptor antagonists (GPI). Bivalirudin and single-drug heparin were compared in the PCI process in a BAT study [2] and ISAR-REACT3 study [3]. Results indicated that severe bleeding significantly decreased more in the bivalirudin group than in the heparin group. Furthermore, bivalirudin and heparin combined with GPI were compared in the REPLACE-2 study. Results indicated that the difference in ischemic events was not significant between these two treatment schemes, while bleeding in the bivalirudin group was reduced by 41% [4]. The subsequent ACUITY study also verified that, in patients with acute coronary syndrome, compared with heparin combined with GPI, single-drug bivalirudin decreased the risk of major bleeding by 47% without increasing ischemic events [5]. The safety of bivalirudin in reducing the risk of bleeding has consistently been confirmed.

However, controversies remain regarding the use of bivalirudin during emergency PCI. The focus of these controversies is whether bivalirudin increases incidence of short-term in-stent thrombosis after PCI. Gregg W. Stone, a professor at Columbia University Medical Center in the United States, discovered in the HORIZONS-AMI study, in 2008 long before the approval of bivalirudin by the FDA, that compared with

heparin+platelet glycoprotein IIb/IIIa receptor antagonists, single-drug bivalirudin in emergency PCI significantly reduced incidence of mortality and adverse event rates within 30 days but increased incidence of acute in-stent thrombosis within 24 hours (1.3% *vs.* 0.3%) [6]. The subsequent EUROMAX study [7] and HEAT-PPCI study [8] considered that bivalirudin increases incidence of early postoperative in-stent thrombosis after PCI.

To avoid postoperative in-stent thrombosis and bleeding after emergency PCI, this present study combined the pharmacodynamics of bivalirudin and multiple antiplatelet agents, commonly used in clinical practice, to innovatively put forward a new approach for bivalirudin, namely, sequential dose therapy. It has obtained ideal effects in clinical practice. To reflect the effects of bivalirudin sequential dose therapy more veritably, this study observed real world clinical practice cases that did not limit the inclusion and exclusion criteria, providing new evidence for clinical treatment decisions.

Patients and methods

Study population

A total of 86 patients admitted to the Cardiovascular Medicine Center, diagnosed with acute STEMI, having undergone emergency PCI, from January 2013 to March 2017, were retrospectively analyzed. All patients received a loading dose of aspirin before surgery. They were divided into two groups: combined clopidogrel group (Group A, *n*=6) and combined ticagrelor group (Group B, *n*=80), according to the combination of clopidogrel or ticagrelor. According to the use of tirofiban during the operation, patients were divided into two groups: combined tirofiban group (Group C, *n*=46) and no combined tirofiban group (Group D, *n*=40). Tirofiban was administered by intracoronary bolus to patients during emergency PCI (10 μg/kg) without intravenous injection. Enrolled patients conformed to diagnostic criteria set forth in G*uidelines for Diagnosis and Treatment of Acute ST-segment Elevation Myocardial Infarction* of the Chinese Medical Association in 2010 [9]. All patients were indicated for emergency PCI and implanted with a rapamycin drug-eluting stent (DES). All patients provided signed informed consent and received bivalirudin sequential dose therapy.

Bivalirudin sequential dose therapy

Patients were intravenously injected with bivalirudin (0.75 mg/kg) (trade name: Taijianing; Salubris Pharmaceuticals Co., Ltd., Shenzhen, China) and received intravenous pumping infusion of high-dose bivalirudin (1.75 mg/kg/h), during and after the operation, until the completion of one tube. Next, patients were treated with continuous intravenous pumping infusion of low-dose bivalirudin (0.2 mg/kg/h) until completion of the second tube. Each tube of bivalirudin contained an effective dose of 250 mg.

Data acquisition

Clinical baseline data, surgery information, and the perioperative antithrombotic plan of patients selected in the present study were extracted from original medical records. Postoperative 30-day adverse events were followed up by telephone or hospital visit.

Observational index and definition

Main observational indexes of the present study included in-stent thrombosis rates and incidence of bleeding events within 30 days postoperatively. Other observational indexes included incidence of major adverse cardiac and cerebrovascular events (MACCE) within 30 days, including secondary myocardial infarction, cardiac death, emergency revascularization, and strokes. Additionally, preoperative and postoperative platelet counts of patients were monitored. In-stent thrombosis was defined by referencing the Bleeding Academic Research Consortium (BARC) definition: occurrence within postoperative 24 hours is regarded as acute in-stent thrombosis and occurrence within 24 hours-30 days is considered as subacute in-stent thrombosis [10]. Furthermore, bleeding events were classified according to the BARC scale [11]. Thrombocytopenia was defined as a decrease in platelet count by more than 50%, compared to baseline or 150×10^9/l. Creatinine clearance was calculated according to the simplified *Modification of Diet in Renal Disease* (MDRD) formula [12].

Statistical analysis

SPSS 21.0 statistical software was used to process data. Normally distributed measurement data are expressed as mean ± standard devia-

Table 1. Basic clinical information of patients

Index	Number of people (n=86)	A group (n=6)	B group (n=80)	*P* value
Female (n, %)	71 (82.6)	6 (100)	65 (80)	0.585
Age (years old)	62.56±12.97	59.83±12.58	62.76±13.05	0.597
Weight (kg)	66.45±11.60	65.00±12.25	66.56±11.63	0.752
Smoke (n, %)	43 (50%)	4 (66.67)	39 (48.75)	0.676
Hypertension (n, %)	50 (58.1)	4 (66.67)	46 (57.50)	0.992
Diabetes mellitus (n, %)	18 (20.9)	2 (33.33)	16 (20.00)	0.601
Dyslipidemia (n, %)	23 (26.7)	4 (66.67)	19 (23.75)	0.042
Creatinine (umol/l)	78.33±28.35	67.17±26.21	76.16±28.49	0.320
eGFR (ml/min.173m^{-2})	104.24±39.99	144.38±80.60	101.23±34.3	0.010
Hemoglobin (g/l)	129.02±17.08	117.33±11.62	129.90±17.15	0.082
Blood platelet count (10^9/l)	171.3±75.5	159.7±60.8	172.2±75.9	0.695

Note: *P*: compared with A and B.

Table 2. Basic clinical information 2 of patients

Index	Number of people (n=86)	C group (n=46)	D group (n=40)	*P* value
Female (n, %)	71 (82.6)	36 (78.26)	30 (87.50)	0.394
Age (years old)	62.56±12.97	62.48±13.37	62.65±12.66	0.952
Weight (kg)	66.45±11.60	69.13±11.70	63.38±10.82	0.021
Smoke (n, %)	43 (50%)	23 (50.00)	20 (50.00)	1.000
Hypertension (n, %)	50 (58.1)	30 (65.22)	20 (50.00)	0.191
diabetes mellitus (n, %)	18 (20.9)	10 (21.74)	8 (20.00)	0.843
Dyslipidemia (n, %)	23 (26.7)	12 (26.09)	11 (27.50)	0.883
Creatinine (umol/l)	78.33±28.35	77.11±27.91	79.73±29.15	0.672
eGFR (ml/min.173m^{-2})	104.24±39.99	102.37±31.71	106.38±48.15	0.646
Hemoglobin (g/l)	129.02±17.08	129.20±17.82	128.83±16.41	0.921
Blood platelet count (10^9/l)	171.3±75.5	164.6±77.2	179.5±68.3	0.349

Note: *P*: compared with C and D.

tion and *t*-test or ANOVA was adopted for intergroup comparisons. Measurement data in skewness distribution are expressed by *M (Q1, Q3)* and were compared between groups by the nonparametric statistic based on of rank-transformation test. Count data are expressed by percentage, while Chi-squared test or Fisher's exact test was adopted for intergroup comparisons. $P<0.05$ is considered statistically significant.

Results

Basic clinical information of patients

A total of 86 patients were enrolled in this study. The average age of these patients was 62.56±12.97 years and average weight was 66.45±11.60 kg. The percentage of males was 82.6%. Furthermore, percentages of patients with hypertension, diabetes mellitus, and dyslipidemia were 58.1%, 20.9%, and 26.7%, respectively (**Tables 1** and **2**).

Bivalirudin sequential dose therapy

Continuous pumping duration of the first-tube high-dose bivalirudin was 1.77 (1.48, 1.95) hours and the continuous pumping duration of the second-tube low-dose bivalirudin was 19.23 (16.67, 20.83) hours.

Coronary angiography and PCI results

A total of 84 patients received PCI, accounting for 97.7% of all patients. All patients underwent stent implantation. Patients that underwent ≥2 implantations accounted for 5.8%. Culprit ves-

Table 3. Patient type of myocardial infarction, culprit vessels, and surgical results

Index	Number of people (n=86)	A group (n=6)	B group (n=80)	C group (n=46)	D group (n=40)
Myocardial infarction					
Antetheca	32 (37.2)	0 (0)	32	18	14
Inferior wall	54 (62.8)	6 (100)	48	28	26
Culprit vessels					
Left anterior descending	32 (37.2)	0	32	18	14
Left circumflex artery	10 (11.6)	6	10	4	6
Right coronary	44 (51.2)	0	38	24	20
TIMI flow after operation					
Grade of 0-1	1 (1.2)	0	1	0	1
Grade of 2	7 (8.1)	1	6	2	5
Grade of 3	78 (90.7)	5	73	44	34

Table 4. Adverse events occurring within 30 days postoperatively

Index	Number of people (n=86)	A group (n=6)	B group (n=80)	*P*# Value	C group (n=46)	D group (n=40)	*P** Value
Stent thrombosis	0	0	0		0	0	
All bleeding	3 (3.49)	0	3	0.629	2	1	0.641
RARC 1-2 grade	3	0	3		2	1	
BRAC 3-5 grade	0	0	0		0	0	
MACCE	2 (2.26)			0.695			0.213
Heart attack again	0	0	0		0	0	
Death	2	0	2		0	2	
Emergency Revascularization	0	0	0		0	0	
Stroke	0	0	0		0	0	
Postoperative thrombocytopenia	2 (2.26)	0	2	0.695	1	1	0.920

Note: P#: compared with A and B; P*: compared with C and D.

sels in 98.8% of patients obtained a thrombolysis in myocardial infarction (TIMI) flow grade of ≥2 after the operation (**Table 3**).

Clinical follow-up results within 30 days

All patients were clinically followed-up within 30 days. No patients had postoperative in-stent thrombosis. Postoperative bleeding occurred in three patients and the total bleeding rate (BARC1-5) was 3.49% (3/86). Furthermore, there were no cases of BRAC 2-5 bleeding. Incidence of MACCE was 2.26% (2/86). Tracing primary medical records, two patients died of postoperative severe heart failure. Incidence of postoperative thrombocytopenia was 2.26% (2/86).

Subgroup analysis revealed that three cases of bleeding occurred in Group B. Incidence in Group A was less than that in the present study. Hence, differences between these two groups were not statistically significant (*P*=0.629). Furthermore, two cases and one case of bleeding occurred in Group C and Group D, respectively, but differences between these two groups were not statistically significant (*P*= 0.641). In addition, there were two cases of death in Group B but differences between these two groups were not statistically significant (*P*=0.695). Two cases of death occurred in Group D, while differences between these two groups were not statistically significant (*P*= 0.213). Moreover, differences in postoperative thrombocytopenia between these two groups were not statistically significant (**Table 4**).

Discussion

In 2016, the FDA released a drug safety statement for bivalirudin, requiring the following content to be added to the new safety label: For

patients with STEMI that received direct PCI, the risk of in-stent thrombosis can be increased by bivalirudin during the early period (within four hours) after PCI, compared with unfractionated heparin (1.2% *vs.* 0.2%). Whether bivalirudin can increase the risk of in-stent thrombosis after PCI has once again caused widespread controversy among medical researchers.

With the progress of many national and international randomized controlled trials regarding the efficacy and safety of bivalirudin, some studies have reported completely different results. Hence, drug use instructions for bivalirudin have been questioned. Primary use instructions for bivalirudin provided by the original research enterprise of bivalirudin, the Medicines (USA), is 0.75 mg/kg (preoperative intravenous bolus), 1.75 mg/kg/h during the operation, and immediate termination after the operation. The EUROMAX and MATRIX study [13] revealed that, based on use instructions provided by the inventor company, the addition of bivalirudin for low-dose maintenance after PCI continued to fail in reducing the risk of acute in-stent thrombosis. A meta-analysis subsequently published by Professor Stone pointed out that acute in-stent thrombosis in patients in the bivalirudin group increased by 1% within 24 hours, compared with that in the heparin+GPI group. This mainly occurred at four hours postoperatively. Differences in incidence of subacute in-stent thrombosis were not significant between these two groups, within 24 hours-30 days [14]. In addition, 1-3 year follow-up results of the HORIZONS-AMI study confirmed that bivalirudin significantly reduced cardiac deaths, all-cause mortality, and severe bleeding rates, compared to those in the heparin group [15, 16]. Further subgroup analysis revealed that cardiac deaths and severe bleeding rates in the bivalirudin group were distinctly reduced, compared to those in the heparin+GPI group [17]. The long-term benefit of bivalirudin is definite but the focus remains on acute in-stent thrombosis after PCI. Many clinicians have carried out useful practices in terms of how to avoid in-stent thrombosis within 24 hours, especially its occurrence within four hours. Academician Yaling Han, of the General Hospital of Shenyang Military Area Command, proposed the therapy of prolonged high-dose infusion after PCI in the BRIGHT study [18]. According to study design, all patients in the bivalirudin group received high-dose continuous infusion for 0.5-4.0 hours (1.75 mg/kg/h) after PCI, confirming that this therapy can effectively reduce incidence of acute in-stent thrombosis. Moreover, it also maintains the advantages of bivalirudin in reducing bleeding and allowing patients to be less prone to thrombocytopenia. In evaluating related literature, Alexander in USA suggested that controversy remains regarding bivalirudin or heparin+GPI, after balancing efficacy, safety, cost, and other factors [19].

There is a clear difference between the use of antiplatelet drugs in emergency PCI patients and elective PCI patients. With the rejuvenation of STEMI onset, a significant number of STEMI patients have not been treated with regular double antiplatelet drug therapy. They have only been administered loading doses of aspirin, clopidogrel, and ticagrelor before emergency PCI. A 300-mg loading dose of aspirin can allow it to reach its peak value in blood serum within approximately 1-2 hours after being taken once. A 300-mg loading dose of clopidogrel can take effect within 6-24 hours and a 600-mg loading dose of clopidogrel can take effect within 2-6 hours. The new antiplatelet drug, ticagrelor, also takes effect within 2-6 hours. However, the half-life of bivalirudin is 25 minutes. The effective serum concentration rapidly decreases when it is stopped. Moreover, the antiplatelet effects of bivalirudin are relatively weak when bivalirudin is stopped early after operation. Furthermore, effective antithrombotic effects are not achieved by clopidogrel and ticagrelor, while postoperative 24 hours is the onset time of acute in-stent thrombosis.

In combining the pharmacodynamics of bivalirudin and commonly used antiplatelet drugs, this present study innovatively proposed bivalirudin sequential dose therapy. Sequential dose therapy, based on prolonging the high dose, adopts continuous intravenous pumping infusion with a low dose, allowing patients to safely spend the first 24 hours free from risk of in-stent thrombosis that can easily occur after emergency PCI. In the present study, no cases of in-stent thrombosis occurred within 30 days, while incidence of total bleeding and MACCE was 3.49% and 2.26%, respectively.

The European retrospective study, EUROVISION, revealed that main bleeding rates and MACCE incidence within postoperative 30 days were 1.6% and 2.9%, respectively [20]. In contrast, in the present study, total bleeding rates were higher and incidence of MACCE was comparable. This may be due to the emergency and elective PCI that occurred at the same time in the EUROVISION study. The present study only included patients with STEMI that underwent emergency intervention. All patients were treated with two kinds of antiplatelet agents with loading doses, increasing the risk of bleeding. However, according to BARC grading on bleeding, there were no cases of BRAC 2-5 bleeding, thereby confirming the safety of bivalirudin during emergency intervention.

In recent years, a new potent antiplatelet drug, ticagrelor, has been widely used in clinical practice. In the present study, the use rate of ticagrelor reached 93.02%. Partial patients with thrombus were treated with intracoronary injections of tirofiban during emergency PCI. According to subgroup analysis, there were no statistically significant differences in terms of total bleeding rates and incidence of MACCE and thrombocytopenia, demonstrating the safety of bivalirudin combined with multiple anticoagulant or antiplatelet drugs.

This study was limited, however, by its single-center design and small sample size. The present results require confirmation through multicenter studies with large sample sizes. Furthermore, there was a certain imbalance in the number of cases, age, gender, and medical history between groups.

The efficacy and safety of bivalirudin, in Chinese patients with STMEI undergoing emergency PCI, was evaluated under present clinical practice conditions. Results demonstrated that bivalirudin sequential dose therapy can effectively control perioperative risk of bleeding in emergency PCI, with good anticoagulant effects. Although these results are affected by various confounding factors, they reflect the present status and actual effects of bivalirudin combined with other multiple anticoagulant or antiplatelet drugs in real-world routine medical treatments. This new usage approach for bivalirudin has been proposed to provide important reference value for clinical decisions.

Disclosure of conflict of interest

None.

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