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The effect of bivalirudin on coagulation function in male patients with coronary heart disease undergoing percutaneous coronary intervention

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Abstract: Aim of this study was to explore the effect of bivalirudin on coagulation function with the treatment of percutaneous coronary intervention (PCI) in male coronary heart disease (CHD) patients. There were 90 male CHD cases treated with PCIas study object and were randomly divided into bivalirudin and unfractionated heparin group (n=45). Unfractionated heparin group patients were given unfractionated heparin and bivalirudin group cases were treated with bivalirudin. Activated clotting time (ACT), thrombin time (TT), prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (Fib), platelet count (PLT) were determined and the major adverse cardiovascular events (MACCE) were observed in two group patients. There was no significant ($p>0.05$) difference with ACT, TT, PT, PLT, APTT and Fib between the two groups before and after 6h, 24h and 72h of operation. The incidence of stent thrombosis and general bleeding with in 24h after PCI in bivalirudin group was lower than in heparin group. After 13 months of follow-up, there was no significant ($p>0.05$) difference in the incidence of MACCE between the two groups. Compared with the treatment of unfractionated heparin in CHD patients after PCI in 24h, the bivalirudin had more remarkable effect, such as rapid onset, short half-life, lower incidence of thrombosis and bleeding.

Keywords: Bivalirudin, general heparin, Coagulation function.

INTRODUCTION

Percutaneous coronary intervention (PCI) has become a major treatment for CHD. In recent years, more and more patients with CHD are willing to receive PCI treatment, but patients after PCI are prone to occur re-infarction and other complications, affects the treatment results (Ito and Ota, 2015; Jing *et al*., 2017). At present, unfractionated heparin is usually given to patients after PCI in the clinical, but the bleeding and other complications after PCI are more common, which are not conducive to the recovery of CHD patients (Hibbert *et al*., 2012).

Bivalirudin is a direct thrombin inhibitor, which exerts anticoagulant effects by directly and specifically inhibiting the activity of factor II A and prolonging the activated clotting time (Abdel-Wahab and Richardt, 2012). Clinical evidence showed that bivalirudin can reduce bleeding events and without increase ischemic events, and could be used as an adjuvant anticoagulant drug for PCI in CHD patients (Gurm *et al*., 2007).

However, there is still lack of relevant data of bivalirudin on the use of PCI in male CHD patients. The purpose of this study is to investigate the effect of the treatment of bivalirudin on coagulation function in male CHD patients with PCI, and to provide valuable guidance for the clinical anticoagulant treatment of male CHD patients with PCI.

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MATERIALS AND METHODS

General data

From January 2016 to July 2016, 90 male CHD patients who were going to receive PCI were chosen as the subjects.

Inclusion criteria

Male patients diagnosed with CHD that underwent PCI.

Exclusion criteria

(1) Patients with anticoagulant contraindications and drug allergy, (2) Patients with history of cerebral infarction less than 6 months, (3) Patients with cerebral infarction occurred more than 2 times.

According to different treatment methods, they were divided into the unfractionated heparin group and the bivalirudin group. There were 45 patients in the unfractionated heparin group having age 41-79 years, with an average age of (63.8+2.4) years. The course of disease was 3-11 years and the average course of disease was (6.4+1.2) years. There were also 45 patients in the bivalirudin group, aged 22-78 years, with an average age of (64.1+2.1) years. The course of disease was 4-12 years and the average course of disease was (6.5+1.5) years.

Methods

For the CHD patients that needed to be treated with PCI, the corresponding drugs were given before coronary angiography. Aspirin 300mg and clopidogrel 300-600mg were used in patients who did not use clopidogrel and aspirin for a long time.

The patients in the unfractionated heparin group were treated with intravenous injection of 100U/kg unfractionated heparin and the ACT of 5min was detected. Additional heparin was added when ACT was less than 225s.

The patients in the bivalirudin group were firstly treated with intravenous injection of 0.75mg/kg bivalirudin (Jiangsu Haosen pharmaceutical Limited by Share Ltd, Zhunzi H20140057), detection of administration of 5min ACT, the additional bivalirudin 0.3mg/kg was added when ACT was less than 225s. Subsequently, continuous intravenous infusion of bivalirudin 1.75mg/(kg. H), was used more than 30min after the end of surgery but not more than 4 hours.

Observation index

The ACT of the two groups was observed before PCI, after 5min of drug injection, immediately after the PCI, 0.5h, 1h and 2h after withdrawing the drug. The blood coagulation indexes such as TT, PT, APTT, Fib and PLT were observed before PCI, and 6h, 24h and 72h after PCI in the two groups. The postoperative bleeding risk of the two groups was observed. The patients were followed up for one month and one year after hospital discharge and the incidence of MACCE was observed in the two groups.

STATISTICAL ANALYSIS

SPSS 22.0 statistical software was adopted for data processing. The comparisons on measurement data between groups was conducted using t test and the data was measured with mean standard deviation (x±s). Enumeration data was expressed in % or chi square test. $P<0.05$ means difference was statistically significant.

RESULTS

Comparison of ACT changes between the two groups

Before the PCI, there was no significant difference of ACT value between the two groups ($P>0.05$). In bivalirudin group, after 5min of bivalirudin injection, postoperative ACT value was higher than the unfractionated heparin group ($P<0.05$). The ACT value in bivalirudin group cases was lower than unfractionated heparin group patients ($P<0.05$), as shown in table 1.

Comparison of blood coagulation indexes between the two groups

There was no significant difference in blood coagulation indexes such as TT, PT, PLT, APTT, Fib between the two groups before PCI and after 6h, 24h and 72h of PCI ($P>0.05$), as shown in table 2.

Comparison of postoperative bleeding risk between the two groups

24h stent thrombosis and bleeding in bivalirudin group patients were lower than unfractionated heparin group cases, the differences were statistically significant ($P<0.05$). There was no statistical significance between the two groups of cerebral hemorrhage ($P>0.05$). As shown in table 3.

Comparison of the Incidence of MACCE between the two groups during follow-up (n, %)

After one month and one year of follow-up, there was no significant difference in the incidence of MACCE between the two groups ($P>0.05$), as shown in table 4.

DISCUSSION

In recent years, the incidence of CHD in men has been increasing year by year and has become one of the major diseases threatening the health of male population (Mehta *et al*., 2004; Suwaidi *et al*., 2001). In CHD patients, age is anindependent risk factors of CHD, because the body is degenerative, with many underlying diseases, myocardial infarction and cardiac arrhythmia of poor tolerance. This is one of the main causes that mortality rate has been increased (Mathey *et al*., 1987; Bakhoum *et al*., 2015; Feizi *et al*., 2017). At present, PCI has become one of the main treatment methods of CHD. The use of anticoagulant and antiplatelet drugs in male CHD patients after PCI and perioperative period can effectively reduce the morbidity and mortality, and improve the effect of PCI treatment (Nikolsky *et al*., 2015; Landes *et al*., 2015). Unfractionated heparin is a traditional medication in CHD patients with PCI and plays a good anticoagulant effect. But bleeding symptoms will be appeared in patients after long time use of heparin as, it is not conducive to the recovery of patients after PCI (Abdel-Wahab and Richardt, 2012). Recent research has confirmed that bivalirudin has a better anticoagulant effect and less side effects (Moulias and Alexopoulos, 2011).

This study mainly investigated the influence of bivalirudin on the coagulation function and safety with PCI in male CHD patients. The results showed that the ACT value of immediate post-PCI and after 5 min of medication in bivalirudin group was significantly higher than that in unfractionated heparin group. In addition, after bivalirudin withdrawal of 1h and 2h in patients, the ACT value was lower than in patients of unfractionated heparin withdrawal. However, there was no significant difference in ACT value between two groups before and after discontinuation of 0.5h. The results revealed that the anticoagulation of bivalirudin was faster and safer than unfractionated heparin. In addition, as a direct thrombin inhibitor, bivalirudin directly played the role of anticoagulation, shortened the half-life.

The coagulation index in the different time before and after PCI in two groups of patients was not significantly different. It followed that both bivalirudin and

Table 1: The changes of ACT in two groups ($\bar{x}$±s) (n=45)

Groups	Pre-PCI	5min after Medication	Immediate Post-PCI	0.5h after Discontinuation	1h after Discontinuation	2h after Discontinuation
Unfractionated Heparin	210.43±24.63	354.5±57.26	355.8±50.51	355.3±58.33	316.6±48.27	262.4±50.35
Bivalirudin	212.4±24.48	592.8±60.47	543.5±64.21	357.8±60.45	240.5±59.21	210.3±42.15
T	0.226	5.571	6.094	7.453	8.005	9.363
P	P≤0.05	P≤0.05	P≤0.05	P≤0.05	P≤0.05	P≤0.05

Table 2: Comparison of blood coagulation indexes between the two groups ($\bar{x}$±s) (n=45)

Groups	Point in time	TT(s)	PT(s)	PLT(×109/L)	APTT(s)	Fib(g/L)
Unfractionated heparin	Pre-PCI	14.4±1.63	9.8±0.56	243.8±48.51	27.3±4.33	3.4±0.27
	6h after PCI	34.4±4.48	12.8±0.47	241.8±36.21	36.8±3.45	2.5±0.54
	24h after PCI	15.12±1.48	10.85±1.63	231.62±47.27	28.42±4.35	3.84±0.15
	72h after PCI	10.15±0.63	3.57±0.62	28.52±4.21	14.29±1.15	3.71±0.19
Bivalirudin	Pre-PCI	13.04±1.15	10.61±0.34	213.78±48.51	27.71±4.10	3.39±20.67
	6h after PCI	33.47±1.23*	12.73±5.16*	212.05±35.61*	36.23±3.95*	2.54±0.71*
	24h after PCI	14.21±0.45*	0.42±0.41*	213.27±43.69*	27.27±4.85*	3.27±0.85*
	72h after PCI	13.38±0.82*	10.34±0.65*	213.06±37.21*	26.98±4.49*	3.27±0.48*

Note: compared with the unfractionated heparin group, (*P≤0.05).

Table 3: The post-PCI bleeding risk of the two groups was compared (n, %)

Groups	24h Stent Thrombosis	General Bleeding	Cerebral Hemorrhage
Unfractionated Heparin	4 (8.9)	10 (22.2)	1 (2.2)
Bivalirudin	1 (2.2)	2 (4.4)	0 (0)
X2	6.218	5.795	0.142
P	P≤0.05	P≤0.05	P≤0.05

Table 4: Comparison of the Incidence of MACCE during Follow-Up (n=45)

		Unfractionated Heparin	Bivalirudin	X2	P
One Month of Follow-Up	Recurrent Angina Pectoris	2 (4.4)	1 (2.2)	0.415	≤0.05
One Year of Follow-Up	Revascularization	2 (4.4)	1 (2.2)	0.415	≤0.05
	Recurrent Angina Pectoris	7 (15.6)	6 (13.3)	1.418	≤0.05
	Recurrent Myocardial Infarction	1 (2.2)	1 (2.2)	0.126	≤0.05
	Cardiac Death	0 (0)	0 (0)	0.006	≤0.05

unfractionated heparin had a good anticoagulant effects in CHD patients with PCI. Heparin is a polysaccharide alternately connected to multimers, anti-clotting effect on patients is very obvious. Bivalirudin also has a powerful anticoagulant effect through inhibiting the activity of thrombin (Group, 2013). The two group patients were all followed up for 1 month and 1 year and the results revealed no difference in MACCE between them after PCI. Moreover, the incidence of 24h stent thrombosis and general bleeding in bivalirudin group was lower than that in the unfractionated heparin group. The reason might be that heparin was probably causing spontaneous bleeding in patients and induced the decrease of platelet count. Therefore, compared to bivalirudin group subjects, the post-PCI bleeding rate was higher in unfractionated heparin patients and the safety of the application of bivalirudin was higher than that of unfractionated heparin (Kim *et al*., 2014).

CONCLUSION

In conclusion, bivalirudin reduced post-PCI bleeding risk, increased safety of anticoagulation, took effect quickly in male CHD patients without increasing the risk of cerebral hemorrhage.

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