Effect of Combining Clopidogrel Bisulfate with Alteplase on Coagulation Function, Neurological Function and Daily Living Ability of Patients with Coronary Heart Disease

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Objective. To explore the effect of combining clopidogrel bisulfate with alteplase on coagulation function, neurological function and daily living ability of patients with coronary heart disease (CHD). **Methods.** The clinical data of 90 CHD patients treated in our hospital from January 2019 to January 2021 were retrospectively analyzed, and the patients were divided into the control group and the study group according to the treatment method, with 45 cases each. The patients in the control group accepted the alteplase thrombolysis treatment, and on this basis, the patients in the study group received the clopidogrel bisulfate treatment, so as to analyze the clinical efficacy of both groups after treatment. **Results.** No statistical differences were observed in the general information between the two groups ($P>0.05$); the overall effective rate of treatment was significantly higher in the study group than in the control group ($P<0.05$); after treatment, various coagulation function indicators in both groups were improved, and PT and APTT were obviously better in the study group than in the control group ($P<0.05$); after treatment, the NIHSS scores of patients in both groups decreased, and the reduction of the study group was significantly greater than that of the control group ($P<0.05$); after treatment, the Barthel indexes of patients in both groups increased, and the increment of the study group was significantly greater than that of the control group ($P<0.05$); during treatment, no controllable serious adverse drug reactions occurred in patients of both groups, and the adverse effects were less severe with a low overall incidence and not significantly different between the two groups ($P>0.05$). **Conclusion.** Combining clopidogrel bisulfate with alteplase can effectively improve the coagulation function in CHD patients, is conducive to promoting the clinical efficacy, and works well in highly effective anti-thrombosis and improvement of patients' neurological function and daily living ability.

Keywords: coronary heart disease (CHD); alteplase; clopidogrel bisulfate; coagulation function

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Coronary heart disease (CHD), also known as coronary atherosclerotic heart disease, is an ischemic heart disease that mostly occurs in adults over the age of 40 years, but more and more younger people also have the disease in recent years. CHD has an urgent onset, rapid progression, and high clinical mortality[1-4]. Currently, the common method for treating CHD in clinic is mainly reperfusion therapy, namely, PCI and thrombolysis[5-6]. Clinical studies have found that, in relative terms, PCI achieves better perfusion, effectively reduces the

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occurrence of complications, and has better outcomes for patients, but in clinical practice, thrombolysis, an easy and cost-effective method that can rapidly achieve vascular reconstruction and effectively improve the left ventricular function in patients, is still necessary in many hospitals because of the limitation of various factors[7-10]. In this context, to reduce the occurrence of various complications, the combination of alteplase and clopidogrel bisulfate was performed in the clinical treatment of CHD patients in our hospital, which obtained significant effect. The results of the study are summarized as follows, so as to make up the data gaps of related studies.

STUDY PROCESS

Patients Screening and Grouping

According to the inclusion and exclusion criteria for patients, 90 eligible patients were screened among the CHD patients treated in our hospital from January 2019 to January 2021, their clinical case data were analyzed, and then 45 of them who received the alteplase thrombolysis treatment were included in the control group, and the rest 45 who accepted the combined therapy of clopidogrel bisulfate and alteplase were included in the study group. The study was approved by the Hospital Ethics Committee.

Inclusion Criteria

① The clinical diagnosis criteria for CHD in the *Guidelines for the Diagnosis and Management of Chronic Stable Angina*[11] were met; ② the patients' age was no more than 75 years; ③ the patients did not have cognitive dysfunction; and ④ the patients and their family members agreed to join the study and signed the informed consent.

Exclusion Criteria

① The patients had other organ or tissue lesions or malignant tumors; ② the patients had heredofamilial hypercholesterolemia; ③ the patients took drugs that affected the blood lipid within 1 month before the study; and ④ the patients were allergic to the drugs used in the study.

Methods

The symptomatic and supportive treatment was given to patients in both groups. In the first hour of intravenous thrombolysis treatment, 60 mg of alteplase (specification: 1 mg/ml; manufactured: Boehringer Ingelheim Pharma GmbH & Co. KG; approval no. S20020034) was administered via intravenous drip, note that 6-10 mg could be administered for the first 1-2 min, then 20 mg was respectively administered in the second and third hours[12-15]. Additionally, the patients in the study group orally took the clopidogrel bisulfate tablets (specification: 25 mg; manufactured: Shenzhen Salubris Parmaceuticals Limited by Share Ltd.; NMPA approval no. H20000542), and for those with unstable angina, the single dosage should be started with 300 mg, then changed to 75 mg daily.

Observation Indexes

The patients' age, gender, heart rate, mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP), plasma clearance (CL), QT dispersion (QTd), disease type, complications such as hypertension, blood lipid abnormality, and diabetes, smoking, and drinking were recorded in detail. It was considered as markedly effective if the frequency of angina decreased by more than 80%, and the ST segment was restored to normal or at least elevated for 0.1 mV; effective if the frequency of angina decreased by 50-80% and the ST segment was restored to 0.05-0.1 mV; and ineffective in case of failure to meet the aforesaid criteria. The overall effective rate = (markedly effective + effective) / total number × 100%.

The patients' coagulation function indicators were measured by the coagulation method, including prothrombin activity (PA), prothrombin time (PT), and active partial thrombin time (APTT). The patients' neurological function before and after treatment was evaluated with the National Institutes of Health Stroke Scale (NIHSS) established by USA National Institutes of Health, covering consciousness, motor, language, sensory, coordinate motor, eye movement, vision, etc. The total score was 42 points, with higher scores indicating more serious nerve defect. The daily living ability of patients before and after treatment was evaluated with the Barthel Index, including feeding, bathing, grooming, dressing, bladder, toilet use, transfers (bed to chair), mobility (on level surfaces), and stairs, with ≤ 40 points indicating totally dependent, 41-60 points indicating partial dependent, 61-99 points indicating minimally dependent, and 100 points indicating independent. The adverse drug reactions occurred in patients of both groups

during treatment were counted.

Statistical Processing

In this study, the data differences were calculated with SPSS22.0, the picture drawing software was GraphPad Prism 7, items included were enumeration data and measurement data, which were examined by X^2 test and t-test, respectively, and differences were considered statistically significant at $P<0.05$.

RESULTS

General Data

No statistical differences in the general data of patients between the two groups were observed ($P>0.05$), which was suitable for the control study. See Table 1.

Table 1

Comparison of patients' general data between the two groups (n=45)

Observation indicator	Control group	Study group	X^2/t	P
Age (years)	68.57±6.392	70.14±6.7	1.136	0.259
Gender (male/female)	31/14	29/16	0.200	0.655
Heart rate (bpm)	77.86±4.538	78.29±5.1	0.419	0.676
MPAP (mmHg)	22.49±3.059	22.57±3.0	0.124	0.902
PCWP (mmHg)	14.72±1.454	14.69±1.4	0.098	0.922
Cl (L/min)	3.45±0.33	3.43±0.31	0.296	0.768
QTd (ms)	50.57±4.432	51.05±4.5	0.509	0.612
Disease type				
Unstable angina	30 (66.67)	31 (68.89)	0.051	0.822
Stable angina	11 (24.44)	9 (20)	0.257	0.612
Acute myocardial infarction	4 (8.89)	5 (11.11)	0.124	0.725

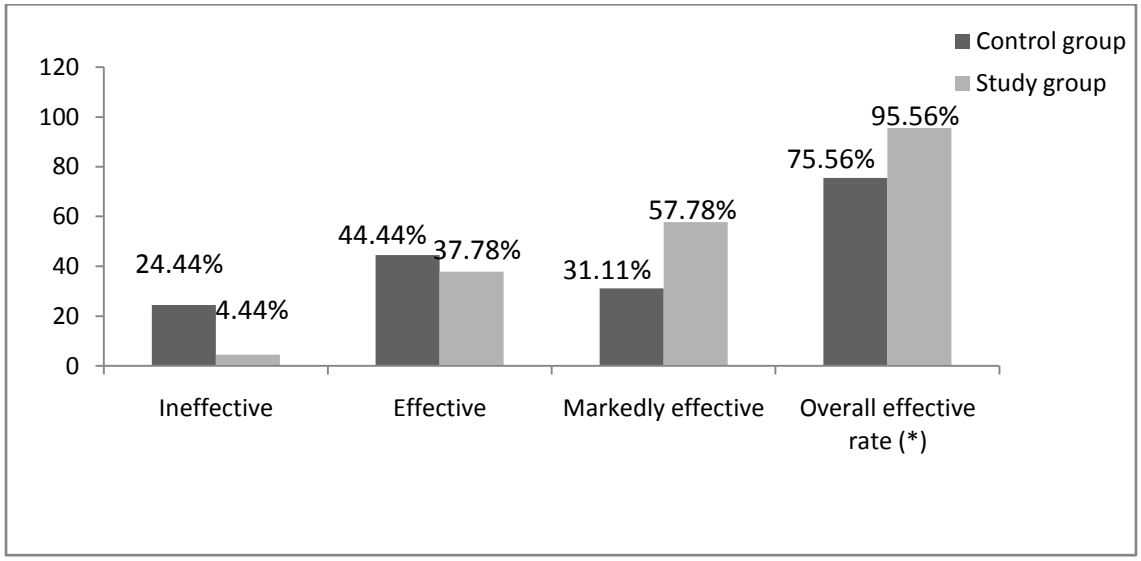
Hypertension	33 (73.33)	31 (68.89)	0.216	0.642
Blood lipid abnormality	27 (60)	28 (62.22)	0.047	0.829
Diabetes	34 (75.56)	37 (82.22)	0.600	0.438
Smoking	25 (55.56)	23 (51.11)	0.179	0.673
Drinking	27 (60)	26 (57.78)	0.046	0.830
Overweight	28 (62.22)	30 (66.67)	0.1940	0.660

Clinical Efficacy

The overall effective rate of treatment was significantly higher in the study group than the control group (P<0.05), see Figure 1 for specific data.

Figure 1

Evaluation of efficacy between the two groups (n=45, %)



Note: The horizontal axis indicated the rating dimensions, and the vertical axis indicated the percentage (%);

There were 11 ineffective cases, 20 effective cases, and 14 markedly effective cases in the control group, and the number of total effective cases were 34;

There were 2 ineffective cases, 17 effective cases, and 26 markedly effective cases in the study group, and the number of total effective cases were 43; and

* indicated that the objective effective rates of patients between the two groups were significantly

different (X^2=7.283, P=0.007).

Coagulation Function

After treatment, various coagulation function indicators of patients in both groups were improved, and PT and APTT were obviously better in the study group than in the control group (P<0.05). See Table 2.

Table 2

Evaluation of patients' coagulation function indicators before and after treatment ($\bar{x}$±s)

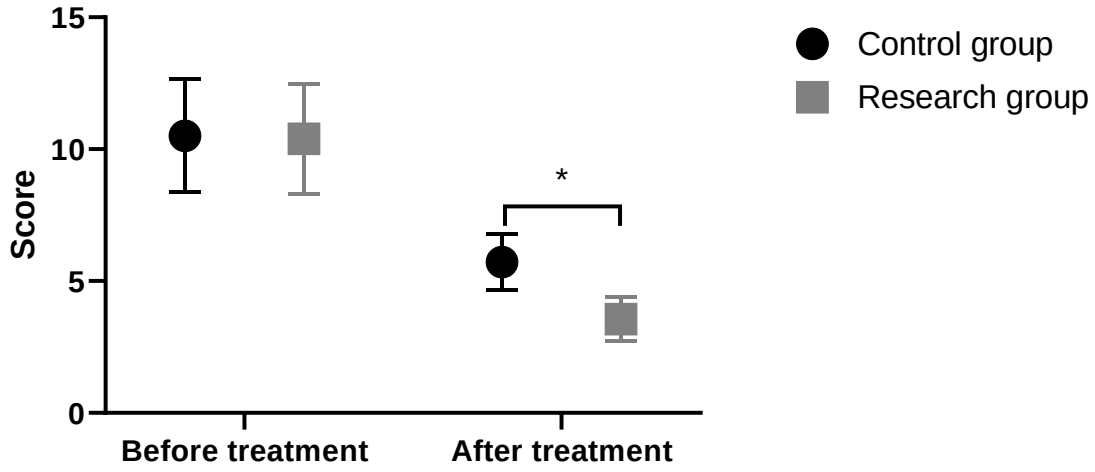
Observation indicator		Control group (n=45)	Study group (n=45)	t	P
PA	Before	0.87±0.05	0.89±0.06		
	After	0.86±0.07	0.87±0.05	0.780	0.438
PT (s)	Before	10.74±0.65	10.77±0.72		
	After	12.32±0.71	13.80±0.63	10.459	<0.001
APTT (s)	Before	33.34±1.32	33.39±1.35		
	After	37.79±1.40	39.67±1.82	5.492	<0.001

Neurological Function

After treatment, the NIHSS scores of patients in both groups decreased, but the reduction was significantly greater in the study group than in the control group (P<0.05). See Figure 2.

Figure 2

Comparison of NIHSS scores of patients between the two groups ($\bar{x}$±s)



Note: The horizontal axis indicated before and after treatment, and the vertical axis indicated the score (points);

Before and after treatment, the NIHSS scores of the control group were (10.51±2.14) and (5.72±1.05), respectively;

Before and after treatment, the NIHSS scores of the study group were (10.39±2.08) and (3.56±0.83), respectively; and

* indicated that the NIHSS scores of patients after treatment between the two groups were significantly different (t=10.826, P<0.001).

Daily Living Ability

After treatment, the Barthel indexes of patients in both groups increased, but the increment was significantly greater in the study group than in the control group (P<0.05), see Table 3.

Table 3

Comparison of patients' Barthel indexes between the two groups ($\bar{x}$±s)

Group	n	Before treatment	After treatment
Control group	45	58.96±4.77	76.80±6.81
Study group	45	60.34±5.63	88.54±7.12
t			7.993
P			<0.001

Adverse reactions

During treatment, no uncontrollable severe adverse drug reactions occurred in patients of both groups, and the adverse effects were less severe with a low overall incidence and not significantly different between the two groups (P>0.05). See Table 4.

Table 4

Statistics of adverse reactions in the two groups [n(%)]

Group	Rash	Nausea	Gastric mucosal bleeding	Total incidence rate
Control group (n=45)	2 (4.44)	1 (2.22)	2 (4.44)	5 (11.11)
Study group (n=45)	1 (2.22)	2 (4.44)	1 (2.22)	4 (8.89)
X^2				0.124
P				0.725

DISCUSSION

CHD usually has an acute onset, rapid progression, a high fatality rate, and more complications, which seriously affects the life health and quality of life of patients and requires early treatment[16-17]. At present, the common method for the treatment of CHD in the clinic is reperfusion therapy, in which intravenous thrombolytic therapy can reduce the mortality rate by performing vascular reconstruction quickly, which is simple and economical[18-20]. To obtain better treatment results and reduce the occurrence of complications, in the treatment of CHD, the combination of intravenous thrombolysis with alteplase and clopidogrel bisulfate was applied in our hospital, obtaining a significantly improved clinical efficacy. At present, there were no reports of combination therapy in the related studies of CHD, so the case data of 90 CHD patients treated in our hospital were retrospectively analyzed to summarize the clinical treatment experience.

Various clinical studies have found that alteplase is a plasminogen activator that can bind plasminogen and fibrin at the thrombus into a ternary complex, excite plasminogen energy to generate plasmin, and then dissolve the thrombus, which does not exert its effect on plasminogen in circulation and thus has a strong local thrombolytic effect. The greatest advantage of alteplase over conventional thrombolytic agents is the greatly reduced probability of hemorrhagic complications in favor of obstructive coronary recanalization[21-24]. Clopidogrel bisulfate, a platelet aggregation inhibitor that selectively inhibits the binding between ADP and platelets, also provokes the activation of ADP mediated glycoprotein complexes as a way to inhibit the occurrence of the platelet aggregation; in addition, the drug also blocks the ADP triggered amplification of platelet activation and effectively inhibits the platelet aggregation problem triggered by other agonists. Therefore, alteplase combined with clopidogrel bisulfate treatment for CHD can effectively achieve dual efficacy and further avoid coronary artery stenosis or occlusion.

The results of the study showed that the overall effective rate of treatment was significantly higher in the study group than in the control group (P<0.05); and after treatment, various coagulation function indicators were improved in patients of both groups, and PT and APTT were obviously better in the study group than in the control group (P<0.05), indicating that with the alteplase venous thrombosis treatment, patients' coagulation function was inhibited, but the effect was more obvious with the combined use of clopidogrel, which was consistent with the study report of JAVAHERI[25]. Besides, after treatment, the NIHSS scores of both groups decreased, but the reduction was significantly greater in the study group than in the control group (P<0.05); the Barthel indexes of both groups increased, and the increment was significantly greater in the study group than in the control group (P<0.05),

which further indicated that compared with applying single thrombolysis therapy, the combined treatment had a better improvement effect on patients' neurological function and daily living ability, and alteplase and clopidogrel worked synergistically in improving patients' microcirculation and recovering from neuronal damage. Finally, the adverse reactions in patients of both groups were analyzed, and it was concluded that during treatment, no controllable serious adverse drug reactions occurred in patients of both groups, and the adverse effects were less severe with a low overall incidence and not significantly different between the two groups ($P>0.05$), indicating that both clopidogrel bisulfate and alteplase were safe and highly-effective.

In summary, under the premise of significant efficacy and safety of drug use, clopidogrel bisulfate plus alteplase is more recommended for the treatment of CHD in this study, which can equalize the use of single drug doses, effectively inhibit the coagulation function of CHD patients, promote the clinical efficacy, and work well in highly effective antithrombotics and improvement of the neurological function and daily living ability of patients. However, this study also has the following deficiencies. ① The follow-up time of this study on patients was short, and the assessment of patient efficacy and safety was limited to a short period of treatment; ② Because of the emergency onset of CHD, rapid diagnosis is required after the patients visited the hospital; for hospitals with emergency PCI conditions, if the first balloon dilatation can be completed in 90 min from arrival to the hospital, AMI patients with acute ST elevation and the onset time within 12 h should be treated with PCI directly, whereas patients with cardiogenic shock should be treated with primary PCI irrespective of the time of onset.

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