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The effect of clopidogrel combined with aspirin on myocardial enzyme, neurohumour and inflammation stress index in patients with myocardial infarction.

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Abstract

Objective: To discuss the clinical effect of clopidogrel combined with aspirin on myocardial enzyme index, neurohumour index and inflammation stress index in patients with Myocardial Infarction (MI).
Methods: We analysed 215 MI patients treated in our hospital from July 2016 to June 2017. 103 MI patients in the control group were treated with aspirin, and 112 MI patients in the observed group were treated with clopidogrel combined with aspirin. The basic clinical data, the results of the lab test, cardiac troponin I (cTn I), Creatine kinase-MB (CK-MB), Noradrenaline (NE), Angiotensin II (AngII), N-terminal pronatriuretic peptide (NT-proBNP), tumor necrosis factor-α (TNF-α), Interleukin 6 (IL-6) and Superoxide Dismutase (SOD) were detected and compared between the two groups.
Results: After treatment for 2 d, the plate aggregation rate induced by ADP 10 μmol/l or 20 μmol/l of patients in the observed group were respectively (7.65 ± 1.08%) with (8.74 ± 1.21%), which were obviously lower than the pre- treatment (P<0.05). The mean serum levels of cTnI and CK-MB were respectively (0.031 ± 0.002 ng/ml) and (19.84 ± 15.76 IU/ml) in the observed group, which were lower than the control group and pre-treatment (P<0.05). Besides, the mean serum levels of NE, AngII, NT-proBNP, TNF-α, IL-6 in the observed group were all lower than the control group and pre- treatment (P<0.05); but the mean serum level of SOD in the observed group was higher than the control group and pre-treatment (P<0.05).
Conclusion: The application of clopidogrel combined with aspirin could be conducive to protect the myocardial cells, inhibit the myocardial enzyme, improve the neurohumour index, and remit the inflammation and stress reaction.

Keywords: Clopidogrel, Aspirin, Myocardial infarction, Myocardial enzyme, Neurohumour.

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Introduction

Currently, cardiovascular disease has been one of diseases with highest lethality and disability rate in the world, especially in the developing countries, it threats individuals' lives and health. As a acute critical illness of coronary heart disease, Myocardial Infarction (MI) has extremely high lethality rate in China. According to the data of World Bank, by 2030, the number of MI patients in China will reach 23,000,000, causing serious financial burden [1,2]. In clinic, anticoagulation and antiplatelet therapies with drugs like clopidogrel and aspirin are commonly used on the basis of thrombolysis, interventional therapy or surgeries. In 2015, Guidelines on the diagnosis and treatment of acute ST-elevation myocardial infarction drafted by Chinese society of cardiology has suggested that if the MI patients have no contraindications, they should receive antiplatelet therapy with aspirin and clopidogrel at the early stage of the disease as soon as possible [3]. However, current basic clinical studies on joint effect of clopidogrel and aspirin in treating myocardial infarction are lack of the support of lab indices. Through observing the impacts of combination of clopidogrel and aspirin on the MI patients' indexes of myocardial enzymes, neurohumour, and inflammation, the present study provides powerful references for medical medication. The details are following.

Materials and Methods

Clinical data

We selected 215 MI patients admitted in our department of cardiology from July 2016 to June 2017, 118 males, 97 females, aged from 48 to 79 y, with a mean age of (62.76 ± 8.15 y).

Inclusion criteria

(1) All participants were eligible the diagnosis standards of Acute Myocardial Infarction (AMI) provided by WHO; (2) the patients first took clopidogrel; (3) the patients or their families signed an informed consent.

Exclusion criteria

(1) Patients were ineligible for the inclusion criteria; (2) the patients suffered from severe consciousness disturbance before the treatment; (3) accompanied by severe liver and kidney dysfunction; (4) accompanied by serious hematological diseases or hemorrhagic diseases; (5) the patients had malignant cancers; (6) the patients had contraindications of clopidogrel or aspirin; (7) the patients suffered severe gastric ulcer; (8) the patients took low molecular heparin; and the rest.

Grouping

All patients were assigned into aspirin group (control group, n=103) and clopidogrel plus aspirin group (observation group, n=112) *via* random number sequence. As to age, sex, Body Mass Index (BMI), history of diabetes, history of hypertension, smoking history, and the findings of routine laboratory tests, both groups were consistent, without statistical difference, P>0.05, Table 1.

Table 1. *Analysis on the clinical data of the patients.*

Group	Cases	BMI (kg/m^2)	Mean age (year)	Sex (case)		History of diabetes (n, %)	History of hypertension (n, %)	Smoking history (n, %)
				Male	Female			
Control group	103	22.57 ± 2.48	62.12 ± 7.73	57	46	29 (28.16)	52 (50.49)	22 (21.36)
Observation group	112	21.98 ± 2.34	63.25 ± 8.24	61	51	27 (24.11)	59 (52.68)	18 (16.07)
χ^2/t	-	1.337	1.458	0.984		1.053	1.174	1.098
p	-	0.315	0.196	0.621		0.462	0.336	0.404

Treatment schemes

(1) Control group: The patients took aspirin (Bayaspirin, provided by Bayer HealthCare Manufacturing S.r.l.) 100 mg/d, at least 12 months; (2) Observation group: on the basis of aspirin 100 mg/d, the patients also took clopidogrel hydrogen sulphate tablets (Plavix, supplied by Sanofi-Synthélabo), loaded with 300 mg first, then 75 mg/d, at least 12 months. (3) All patients were injected low molecular heparin 5000 μ, twice a day, for 7 d. In addition, they all were given routine therapies based on their conditions, including α-adrenergic receptor blocking agents, nitroglycerin, angiotensin-converting enzyme inhibitors, diuretics, and calcium antagonists, etc.

Observation indexes of experimental methods

Take blood samples: Before therapy and after 2 d's treatment, all participants under fasting were collected venous blood in the morning, and the blood samples separated by centrifugation were stored at -20°C [4,5].

Testing of coagulation conditions: The platelet accumulations at baseline and after 2 d therapy were tested.

Testing of myocardial enzyme: Myocardial damage markers such as cardiac troponin I (cTn I) and Creatine Kinase-MB (CK-MB) were measured using a full-automatic immunofluorescence chemiluminescent analyzer (IMMULITE system) and original kit. cTnI and CK-MB kits were bought from Nanjing Getein Bio-Pharmaceutical Co., Ltd.

Testing of nerve and body liquid indices: Neurohumour indexes in serum like Noradrenaline (NE), Angiotensin (AngII), N-terminal pronatriuretic peptide (NT-proBNP) were tested by enzyme-linked immunosorbent assay (ELISA) kit. ELISA kit was bought from Shanghai Helong Bio-technology Co., Ltd.

Testing of inflammation stress index: The level of tumor necrosis factor-α (TNF-α) and Interleukin 6 (IL-6) in serum were detected by ELISA kit; meanwhile, the level of Superoxide Dismutase (SOD) was examined by radio immunoassay. TNF-α ELISA and IL-6 ELISA kits are bought from Shanghai Helong Bio-technology Co., Ltd. SOD radioimmunoassay kit was purchased from Shanghai Radioimmunoassay Technology Research Institute. The above testing methods were in accordance with the inserts of the kits.

Statistical analysis

All data were analysed by software SPSS22.0. The measurement data were processed with t test, while the enumeration data were analysed with chi square test. P<0.05 was considered statistically significant.

Results

Changes of the platelets accumulation in the patients of two groups

Before treatment, the rate of platelets accumulation after 10 μmol/l and 20 μmol/l ADP induction in the patients of the control group was (12.18 ± 3.43%) and (14.26 ± 3.99%), respectively, while that in the patients of the observation group was (11.94 ± 2.77%) and (13.97 ± 2.53%) separately, having no statistical difference, P>0.05. After treatment, the rate of platelets accumulation with 10 μmol/l and 20 μmol/l ADP induction in the patients of the observation group was 7.65 ± 1.08% and 8.74 ± 1.21% in separate, which was lower than that before treatment, with a significant difference, P<0.05;

However, when compared the patients in the control group, there was no difference, P>0.05, Table 2.

Table 2. *Platelets accumulation in the patients of two groups ($\bar{x}$ ± s).*

Group	ADP (10 μmol/l)				ADP (20 μmol/l)			
	Before treatment	2 d after treatment	t1	p1	Before treatment	2 d after treatment	t1	p1
Control	12.18 ± 3.43	8.81 ± 2.54	5.683	0.013	14.26 ± 3.99	9.48 ± 2.19	7.412	0.001
Observation	11.94 ± 2.77	7.65 ± 1.08	4.296	0.018	13.97 ± 2.53	8.74 ± 1.21	7.005	0.001
t2	0.974	1.044	-	-	1.153	1.167	-	-
p2	0.651	0.316	-	-	0.189	0.164	-	-

Comparison on the myocardial enzyme indexes of the patients in two groups

Compared two groups before treatment, there was no statistical difference in serum cTnI and CK-MB level (P>0.05). After 2 d treatment, the level of cTnI and CK-MB in the patients of the observation group decreased by (0.031 ± 0.002 ng/ml) and (19.84 ± 15.76 IU/ml) respectively, which was lower than the mean level of cTnI and CK-MB in the those of the control group, P<0.05; And compared with the level before treatment, the difference was also significant, P<0.05, Table 3.

Table 3. *Comparison on the patients' myocardial enzyme indexes ($\bar{x}$ ± s). Note: t1 and p1 refer to the comparison between the values before treatment and 2 d after treatment; t2 and p2 refer to the comparison between observation group and control group.*

Group	cTn (ng/ml)				CK-MB (IU/ml)			
	Before treatment	2 d after treatment	t1	p1	Before treatment	2 days after treatment	t1	p1
Control group	0.078 ± 0.002	0.046 ± 0.002	8.742	0.001	56.32 ± 21.78	30.18 ± 22.63	3.867	0.034
Observation group	0.074 ± 0.001	0.031 ± 0.002	10.317	0.001	60.47 ± 29.65	19.84 ± 15.76	6.772	0.009
t2	1.143	3.028	-	-	1.004	2.625	-	-
p2	0.301	0.036	-	-	0.418	0.041	-	-

Comparison on the neurohumour indexes of the patients in two groups

After 2 d treatment, the levels of NE, AngII, and NT-proBNP in the patients of the observation group were much lower than that of the control group and that of the pretreatment, with a statistical difference, P<0.05, Table 4.

Table 4. *Comparison on the patients' neurohumour indexes ($\bar{x}$ ± s). Note: t1 and p1 refer to the comparison between the values before treatment and 2 d after treatment; t2 and p2 refer to the comparison between observation group and control group.*

Group	NE (ng/L)		AngII (ng/L)		NT-proBNP (ng/L)	
	Before treatment	2 d after treatment	Before treatment	2 d after treatment	Before treatment	2 d after treatment
Control group	411.76 ± 148.53	296.53 ± 66.27	5.072	0.008	167.43 ± 43.46	80.66 ± 31.14
Observation group	402.89 ± 126.48	231.02 ± 42.58	9.386	0.001	151.89 ± 27.55	54.37 ± 28.11
t2	0.855	2.182	-	-	0.899	1.976
p2	0.689	0.048	-	-	0.576	0.049
Group	**NE (ng/L)**		**AngII (ng/L)**		**NT-proBNP (ng/L)**	

	Before treatment	2 d after treatment	t1	p1	Before treatment	2 d after treatment	t1	p1	Before treatment	2 days after treatment	t1	p1
Control group	411.76 ± 148.53	296.53 ± 66.27	5.072	0.008	167.43 ± 43.46	80.66 ± 31.14	4.264	0.029	316.51 ± 171.82	209.42 ± 143.91	4.924	0.018
Observation group	402.89 ± 126.48	231.02 ± 42.58	9.386	0.001	151.89 ± 27.55	54.37 ± 28.11	4.815	0.027	307.45 ± 182.67	117.88 ± 76.54	8.976	0.001
t2	0.855	2.182	-	-	0.899	1.976	-	-	0.923	7.252		
p2	0.689	0.048	-	-	0.576	0.049	-	-	0.486	0.004		

Comparison on the inflammation indexes of the patients in two groups

After 2 d treatment, compared with the control group and the pretreatment, the levels of TNF-α and IL-6 in the patients of the observation group were much lower, but the level of SOD increased much, with a statistical difference, P<0.05, Table 5.

Table 5. Comparison on the patients' inflammation indexes ($\bar{x} \pm s$). Note: t1 and p1 refer to the comparison between the values before treatment and 2 d after treatment; t2 and p2 refer to the comparison between observation group and control group.

Group	TNF-α (ng/l)				IL-6 (ng/l)				SOD (IU/ml)			
	Before treatment	2 d after treatment	t1	p1	Before treatment	2 d after treatment	t1	p1	Before treatment	2 d after treatment	t1	p1
Control group	18.19 ± 4.62	14.28 ± 3.45	4.008	0.031	200.75 ± 87.63	167.49 ± 43.85	3.186	0.038	75.48 ± 23.14	96.52 ± 28.17	1.359	0.051
Observation group	17.86 ± 3.17	10.06 ± 3.83	4.746	0.023	192.59 ± 91.34	113.46 ± 28.04	5.273	0.025	78.32 ± 19.85	131.19 ± 34.86	5.862	0.011
t2	0.516	1.997	-	-	0.615	2.237	-	-	0.662	5.772		
p2	0.881	0.049	-	-	0.422	0.044	-	-	0.420	0.024		

Discussion

As one of cardiovascular diseases harming humans' health severely, coronary heart disease has high mortality and disability rate with complex etiologies, augmenting heavy financial burden to the patients' families. While acute myocardial infarction has been one of the key causes for the death of the patients with coronary heart disease, which is closely related to the thrombosis due to the rupture of unstable coronary plaques [6-8]. Once the plagues rupture, platelets will accumulate rapidly and develop into pale thrombus, which usually leads to non ST-Segment Elevation Myocardial Infarction (NSTEMI); if the rupture is serious, a massive adherent fibrin will form red thrombus, resulting into coronary total occlusions and ST-Segment Elevation Myocardial Infarction (STEMI) [9,10]. Presently, in term of the aim of treating MI, the first thing is to recover the hemoperfusion of coronary artery as soon as possible, but antithrombotic prophylaxis is also essential. And the combination of clopidogrel and aspirin is the gold standard for preventing the patients with coronary heart disease from major adverse cardiovascular events [11].

Aspirin, a traditional antiplatelet drug, mainly acts on cyclooxygenase and inhibits the transformation pathway of Arachidonic Acid (AA) to achieve antithrombotic prophylaxis [12]. While clopidogrel, a new antiplatelet aggregation drug pertaining to athiophene pyridine derivatives, commonly, blocks inreversiblely diphosphate creatinine receptor to control the combination of fibrinogen and GPIIb/IIIa receptor, so as to restrain antiplatelet aggregation [13,14]. Some research reveals that aspirin alone is not great enough for rescuing MI patients, and clopidogrel has better clinical efficacy in improving th prognosis of cardiac ischemic events than aspirin [15]. In this study, we combine clopidogrel with aspirin to treat MI patients. After 2 d treatment, the rate of platelets aggregation with 10 μmol/l and 20 μmol/l ADP induction in the patients of the observation group was lower than that before treatment, with a significant difference, P<0.05; however, when compared the patients in the control group, there was no difference, P>0.05. That suggests that clopidogrel doesn't enhance the effect of aspirin on restraining antiplatelet aggregation induced by ADP. What's more, after 2 d treatment, the levels of myocardial enzyme indexes like cTnI and CK-MB are lower than that of the control group and that of the pretreatment, and the level of neurohumour indexes such as NE, AngII, NT-proBNP and that of inflammation indexes including TNF-α and IL-6 likewise (P<0.05); while the levels of oxidative stress indexes like serum SOD in the observation group are higher than that in the control group and that before treatment (P<0.05).That shows that clopidogrel and aspirin have synergetic effects on the platelets accumulation induced by collagen and myocardial

enzymes, and it can improve the degree of myocardial cell injury, participate in the physiological processes like myocardial remodeling and vasoconstriction, and ameliorate the neurohumour indexes. The major markers for the diagnosis of myocardial necrosis are cTnI, CK-MB, and the like [16]. It was believed that CK-MK was the gold standard for diagnosing coronary heart disease, but with recent advances in diagnostic methods and detections, cTnI has been considered to be more sensitive and specific than CK-MB. After 2 d treatment, the levels of cTnI and CK-MB of the patients in the observation are less than that in the control group, indicating that the combination of clopidogrel and aspirin has stronger protective effects on myocardium and decreases the releases of myocardial enzymes. Sympathetic nervous system and Renin-Angiotensin-Aldosterone System (RAAS) refer to two major systems maintaining vascular tone, there into, NE, AngII, and NT-proBNP are main neuroendocrine factors involving the regulation of vascular tone, particularly, NT-proBNP has always been one of the most important and sensitive indexes detecting the severity of heart failure in clinic [17]. Compared with the control group, the levels of NE, AngII, and NT-proBNP of patients in the observation after treatment are lower, which suggests that the combination of clopidogrel and aspirin can significantly improve the patients' neurohumour indexes. SOD activity indirectly reflects the ability of free radical elimination. After 2 d treatment, the level of serum SOD of the patients in the control group raises, while the levels of inflammation factors such as TNF-α and IL-6 reduce, showing that the inflammation cells gets controlled and the activity of matrix metalloproteinase cuts down, so as to abate the thinning tendency of fibrous cap and augment the stability of atherosclerotic plaques.

In a word, for the treatment of MI, the combination of clopidogrel and aspirin helps to protect myocardial cells, reduces the release of myocardial enzymes, improves the neurohumour indexes, and relieves inflammatory responses and oxidative stress reactions, with a wide prospect of clinical application.

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