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Original Article

Aspirin plus clopidogrel for angina pectoris in coronary heart disease patients

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Abstract: Objective: To explore the efficacy of the combination of aspirin and clopidogrel for angina pectoris in patients with coronary heart disease (CHD) and its underlying mechanisms. Methods: From January 2017 to February 2018, 80 CHD patients with angina pectoris who had been hospitalized in Zhuji People's Hospital of Zhejiang Province were recruited in this study. The enrolled patients were randomly divided into the observation group (n=40) and the control group (n=40). In addition to usual care, the patients in the control group received aspirin alone, while those in the observation group received aspirin-clopidogrel treatment for 1 month. The two groups were compared in the treatment effect of angina pectoris, and changes in serum inflammatory factors, plasma viscosity, concentration of plasma fibrinogen and whole blood viscosity, cardiac function, and adverse events. Results: The rate of overall response of angina pectoris was 92.5% in the observation group, which was substantially higher than 72.5% in the control group (P=0.039). At the end of the treatment, IL-6 and TNF-α levels in the observation group were remarkably lower than those in the control group (both P<0.001); the plasma viscosity, concentration of plasma fibrinogen and whole blood viscosity were also significantly lower (t=5.262, P<0.001; t=7.589, P<0.001; t=5.311, P<0.001;), with statistically significant between the two groups. Additionally, the left ventricular ejection fraction (LVEF) in the observation group was significantly higher than that in the control group (P=0.001), but the left ventricular end-diastolic diameter (LVDD) was significantly smaller (P=0.034). No significant between-group difference was seen in the rate of overall adverse events (P=0.479). Conclusion: The combination of aspirin and clopidogrel was effective in treating angina pectoris of CHD patients, leading to fewer adverse events. This might be associated with improved plasma viscosity and cardiac function, as well as lower IL-6 and TNF-α levels.

Keywords: Aspirin, clopidogrel, coronary heart disease, angina pectoris

Introduction

Angina pectoris in coronary heart disease (CHD) patients is clinically the most common cardiovascular disease, with high morbidity and mortality and a serious threat to our human health [1, 2]. The pathogenesis of angina pectoris may be lack of blood supply in myocardium on account of coronary stenosis, which further results in precordial pain due to transient ischaemia-hypoxia [3, 4]. Clinically, medical therapy is primarily used for the treatment of angina pectoris, and the efficacy and prognosis vary greatly with different drugs [5]. Aspirin is the preferred drug for CHD [6]. It can effectively inhibit vasoconstriction and platelet aggregation, preventing and controling thrombosis [7]. However, aspirin use has shown to lead to gastric mucosal injury, and its monotherapy has poor efficacy [8, 9]. Clopidogrel, a thienopyridine antiplatelet agent, irreversibly inhibits platelet aggregation. Previous studies have demonstrated that clopidogrel can effectively prevent and treat CHD and myocardial infarction [10, 11]. Nevertheless, the efficacy and mechanisms of action of aspirin-clopidogrel therapy in the treatment of angina pectoris remain unclear. Therefore, the present study was aimed to explore the effect of aspirin-clopidogrel combination in the treatment of angina pectoris in CHD patients and its underlying mechanisms, providing supportive evidence for clinical treatment of the disease.

Materials and methods

Subjects

Eighty CHD patients with confirmed angina pectoris who had hospitalized in Zhuji People's

Table 1. Basic data of patients

Variable	Observation group	Control group	t/χ^2	P
Case (n)	40	40		
Male/Female	27/13	30/10	0.549	0.459
Age (year)	57.4±5.8	59.2±6.1	1.352	0.180
Course of disease (year)	3.4±0.5	3.5±0.6	0.810	0.421
Underlying disease (n)				
Hypertension	27	24	0.487	0.485
Diabetes	20	22	0.201	0.654
Hyperlipidemia	17	15	0.208	0.648
Angina class			0.585	0.900
I	6	8		
II	15	16		
III	11	9		
IV	8	7		

Hospital of Zhejiang Province from January 2017 to February 2018 were enrolled in this study. In terms of a random number table, they were classified into an observation group and a control group, with 40 in each group. The patients in the observation group underwent dual antiplatelet therapy with aspirin plus clopidogrel, whereas those in the control group were given aspirin alone. Inclusion criteria for this study were the following: an age of 18 years or more; patients meeting the diagnostic criteria for angina pectoris: clinical manifestations of precordial paroxysmal or crushing pain which was located in the back of the sternum, associated with radiating pain and each attack of 3 to 5 minutes, and the pain could be relieved after rest or taking nitrates; objective evidence of myocardial ischemia including ST-T segment changes on electrocardiography, positive exercise stress test, or positive coronary angiography [12]. Exclusion criteria were the following: anticoagulant therapy in the previous month, hypersensitivity to aspirin or clopidogrel; severe arrhythmia, acute myocardial infarction and severe hepatic and renal insufficiency; diseases with ST-T segment changes on electrocardiography caused by electrolyte disturbance, cardiac hypertrophy and bundle branch block; secondary myocardial ischemia arising from hyperthyroidism, anemia, aortic stenosis, and hypertrophic cardiomyopathy. This study got approval from the Ethics Committee of Zhuji People's Hospital of Zhejiang Province, and patients and their families gave written informed consent.

Treatment

Enrolled patients were classified into an observation group and a control group in terms of a random number table, with 40 patients in each group. All patients received usual care which included bed rest, oxygen inhalation, oral betaloc for control of ventricular rate, oral lipitor for adjustment of blood lipid levels and stabilization of atherosclerotic plaques, oral Norvasc and other medications administered to patients with hypertension to control blood pressure, and oral metformin and other drugs administered to patients with diabetes to control blood glucose. In addition to usual care, patients in the control group received oral aspirin enteric-coated tablets (at a dose of 100 mg once daily; code NMPN J20130078, Bayer HealthCare Manufacturing S.r.l). Patients in the observation group were given dual antiplatelet therapy with aspirin and clopidogrel on the basis of usual care. The dose of aspirin matched with that of the control group, and clopidogrel was administered orally at a dose of 75 mg once per day (code NMPN J20130083, Sanofi Winthrop Industrie, France). The treatment duration for both groups was one month. During the treatment period, none of patients in both groups discontinued or withdrew from the study due to side effects of aspirin or clopidogrel.

Outcome measures

The clinical response to treatment was compared between the two groups. The criteria for clinical response were as follows: A patient had no response when the frequency of angina pectoris was dropped by less than 50%, without improved ECG; the patient had partial response when the frequency of angina pectoris was dropped by less than 50%-80%, with significantly improved ECG; the patient had complete response when the frequency of angina pectoris was lowered by more than 80%, and ECG returned to normal [13]. Overall response rate of angina treatment = (Number of partial and complete response cases)/Total number of cases * 100%.

The serum inflammatory factors were compared between the two groups: venous blood (3

Table 2. Clinical response to angina treatment

Variable	Case (n)	No response	Partial response	Complete response	Overall response rate (%)
Observation group	40	3	13	24	92.5
Control group	40	11	10	19	72.5
χ^2					4.242
P					0.039

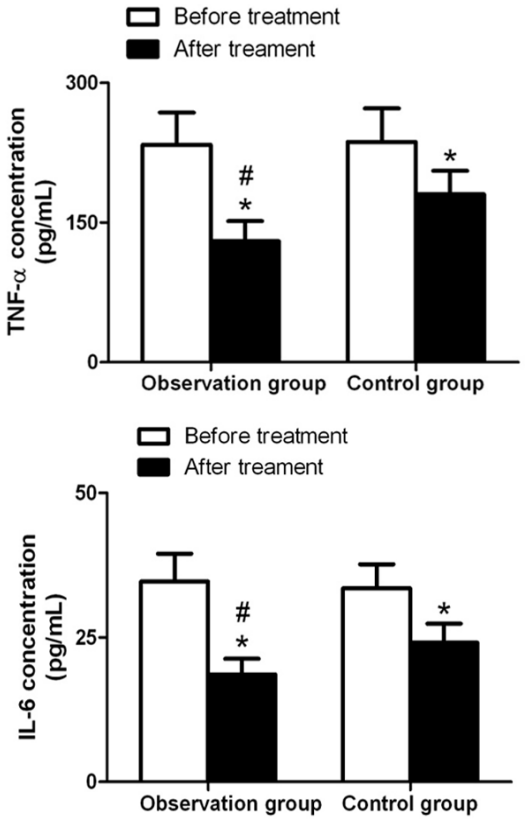

Figure 1. Comparison of serum IL-6 and TNF-α levels between the two groups. *P<0.001, compared with before treatment in the same group; #P<0.001, compared with the control group.

mL) was collected from cubital vein of each patient before and at the end of treatment, centrifuged at 2000 r/min for 10 minutes. The supernatent was collected and stored at -20°C for use. Serum IL-6 and TNF-α levels were tested with the enzyme-linked immunosorbent assay (ELISA). The ELISA kits for IL-6 and TNF-α were purchased from R&D systems, USA. The procedures were performed strictly in accordance with the instructions on the kits.

The plasma viscosity, concentration of plasma fibrinogen, and whole blood viscosity were compared between the two groups. Concentration of plasma fibrinogen was tested with a blood coagulation analyzer, whereas plasma viscosity and whole blood viscosity were detected using an automated blood rheometer.

The two groups were compared in cardiac function. Before treatment and at the end of treatment, left ventricular end-diastolic diameter (LVDD) and left ventricular ejection fraction (LVEF) were tested by means of color Doppler echocardiography.

The rates of adverse events were compared between the two groups. Adverse events included gastric mucosal injury, gastrointestinal bleeding, acute myocardial infarction, and recurrent angina.

Statistical analysis

All data were analyzed with SPSS statistical software, version 21.0. Measurement data were represented as mean ± SD. Between-group comparisons were made using an independent sample t test, while intragroup comparisons before and after treatment were conducted by a paired t-test. Count data was expressed as rates, and comparisons were performed with the chi-square test. P<0.05 was considered statistically significant.

Results

Basic data of patients

No significant differences were noted between the two groups in age, gender, course of disease, underlying disease, and angina pectoris (**Table 1**).

Clinical response to treatment

Among patients with angina pectoris, the overall response to treatment was significantly different between the observation group and the control group (92.5% vs 72.5%; χ^2=4.242, P=0.039), as shown in **Table 2**.

Serum IL-6 and TNF-α levels

Insignificant difference was noted between the two groups in IL-6 and TNF-α levels before

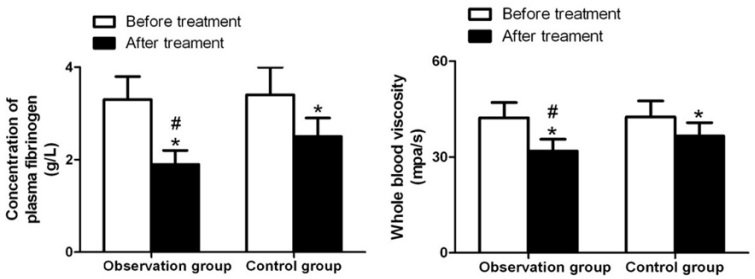

Figure 2. Comparison of plasma viscosity, concentration of plasma fibrinogen and whole blood viscosity between the two groups. *P<0.001, compared with before treatment in the same group; #P<0.001, compared with the control group.

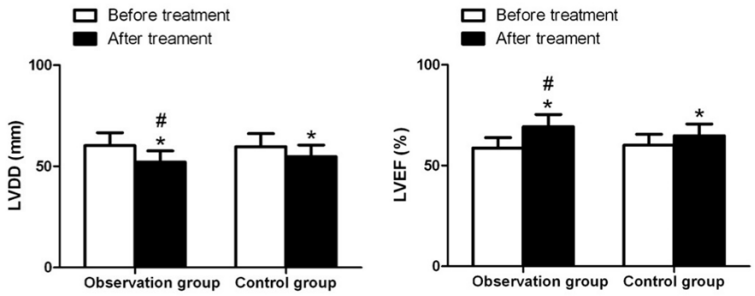

Figure 3. LVDD and LVEF in the two groups. *P<0.001, compared with before treatment in the same group; #P<0.001, compared with the control group.

treatment. In both groups, the levels of IL-6 and TNF-α after treatment were remarkably lower than those before treatment (both P<0.001). At the end of treatment, the levels of IL-6 and TNF-α were substantially lower in the observation group than in the control group (t=8.158, P<0.001; t=9.623, P<0.001; **Figure 1**).

Plasma viscosity, concentration of plasma fibrinogen and whole blood viscosity

No significant difference was seen in plasma viscosity, plasma fibrinogen content and whole blood viscosity before treatment between the two groups. Plasma viscosity, plasma fibrinogen content and whole blood viscosity in both groups were strikingly lower after treatment than before treatment (all P<0.001). At the end of treatment, plasma viscosity, plasma fibrinogen content and whole blood viscosity were significantly lower in the observation group than in the control group (t=5.262, P<0.001; t=7.589, P<0.001; t=5.311, P<0.001; **Figure 2**).

LVDD and LVEF of patients

LVDD and LVEF values before treatment were insignificantly different between the two groups. For patients in both groups, LVEF values after treatment were remarkably higher than before treatment, with significantly lower LVDD values (both P<0.001). At the end of treatment, LVEF in the observation group was higher than that in the control group (t=3.381, P=0.001), but LVDD was lower (t=2.156, P=0.034; **Figure 3**).

Adverse events of patients

The percentage of patients with adverse events was 15% (6/40) in the observation group, as compared with 7.5% (3/40) in the control group. There was insignificant difference in the percentage of patients with adverse events between the two groups (P=0.479; **Table 3**).

Discussion

Over the years, angina pectoris has been increasingly prevalent in CHD patients on a yearly basis. It is acute and recurrent. Myocardial infarction, and even sudden death may occur if patients are not treated in time [14]. Aspirin is the most commonly used drug for the treatment of angina pectoris. It achieves antithrombotic effects by inhibiting cyclooxygenase. Clopidogrel is an adenosine diphosphate receptor antagonist that selectively inhibits ADP binding to platelet receptors and inhibits activation of the glycoprotein GPIIb/IIIa complex, thereby achieving platelet aggregation. The combination of aspirin and clopidogrel can improve anti-platelet aggregation and prevent cerebral embolism, reducing the incidence of stroke [15, 16]. In the present study, we investigated the effect of aspirin plus clopidogrel in

Table 3. Adverse events of patients

Variable	Case (n)	Gastric mucosal injury	Gastrointestinal bleeding	Acute myocardial infarction	Recurrent angina	Overall adverse events rate
Observation group	40	2	4	0	0	15% (6/40)
Control group	40	1	1	1	0	7.5% (3/40)
χ^2						0.501
P						0.479

the treatment of angina pectoris in CHD patients. We found that the overall response rate of aspirin-clopidogrel therapy for angina pectoris was 92.5%, significantly higher than that of aspirin monotherapy, and there was no statistically significant difference between the two groups in the percentages of patients who had adverse events, which was consistent with the findings reported by Peters et al. [17].

The pathogenesis of angina pectoris is still unclear. Increasing studies have confirmed that coronary atherosclerosis and thrombosis are the pathological basis for the presence and development of angina pectoris [18, 19]. Hypercoagulability, abnormal fibrinolysis, platelet activation, and increased fibrinogen synthesis all contribute to the presence of thrombosis [20]. The current study revealed significantly lower plasma viscosity, concentration of plasma fibrinogen, and whole blood viscosity in patients assigned to aspirin and clopidogrel than those assigned to aspirin alone, indicating that clopidogrel-aspirin can exert the synergistic effect and improve the inhibition of platelet aggregation by aspirin. These findings are similar to those reported by Chaturvedula et al. [21]. Inflammatory reactions occur in the whole course of coronary atherosclerosis. A large number of inflammatory mediators may damage the extracellular matrix and promote platelet activation, leading to thrombosis; if severe enough, acute myocardial infarction may occur [22]. TNF-α may damage vascular endothelial cells, cause vascular dysfunction, and promote thrombosis, eventually resulting in ischemia and hypoxia, or even necrosis [23, 24]. IL-6 is primarily secreted from mononuclear macrophages and Th2 cells. IL-6 levels can be used for prediction of angina pectoris, as elevated IL-6 levels and unstable coronary atherosclerotic plaques are closely associated with the incidence of cardiovascular events [25]. The current study showed that IL-6 and TNF-α levels in patients with aspirin plus clopidogrel were strikingly lower than those in patients with aspirin alone. Although clopidogrel has no direct anti-inflammatory effect, it can exert an indirect anti-inflammatory effect by inhibiting platelet activation and reducing vein wall and plasma P-selectin levels [26]. Therefore, aspirin combined with clopidogrel can significantly inhibit serum IL-6 and TNF-α levels in CHD patients with angina pectoris. Additionally, when it comes to cardiac function, patients had better cardiac function with aspirin-clopidogrel than with aspirin monotherapy. Patients in the observation group had considerably higher LVEF levels, but lower LVDD levels than those in the control group, showing aspirin-clopidogrel therapy is effective in improving cardiac functions in patients, which is consistent with that reported by Khosravi et al. [27].

In conclusion, in CHD patients who had angina pectoris, aspirin-clopidogrel therapy was associated with a better therapeutic effect, fewer adverse events, a more excellent anticoagulant effect, lower serum IL-6 and TNF-α levels and improved cardiac function. Hence, it is worthy of clinically extensive application. However, there are some limitations in this study, such as a small sample size, a study of single-center nature and absence of long-term follow-ups. Multi-center studies with larger sample size and longer-term follow-ups are needed for further validation.

Disclosure of conflict of interest

None.

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