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Effect of Clopidogrel Combined with Atorvastatin on Serum Lipids, Inflammatory Factors and Cardiac Function Parameters in Patients with Angina Pectoris and Coronary Heart Disease

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JM and JJ conducted the experiments in this study. JM and LS contributed to the design and interpretation of the current study and wrote the article. All authors read, revised, and approved the final manuscript.

Key words
Clopidogrel, Atorvastatin, Angina pectoris, Coronary heart disease, Serum lipid, Inflammatory factors

ABSTRACT

The objective of this study was to analyze the regulatory effect of Clopidogrel combined with Atorvastatin on the low-density lipoprotein cholesterol (LDL-C), triacylglycerol (TG), and total cholesterol (TC) in patients with angina pectoris and coronary heart disease. Eighty-three patients admitted to a hospital from January 2021 to December 2022 are research subjects. The enrolled patients are randomly numbered 1-83. Patients with odd numbers (42 cases) and even numbers (41 cases) are included in the control group (CG) and the observation group (OG), respectively. On the basis of routine treatment, the CG patients are treated with low molecular weight heparin and aspirin. The OG are treated with Clopidogrel and Atorvastatin. The changes in serum lipids, inflammatory indicators, and cardiac function are compared between the two groups before the treatment (Time 0), after 2 weeks of the treatment (Time 1), and after 4 weeks of the treatment (Time 2). There is no significant distinction in serum lipid, inflammatory indicators, and cardiac function between groups at Time 0 (P>0.05). While the serum lipids and inflammatory indicators levels at Time 1 and Time 2 are below those at Time 0and the levels at Time 2 are lower than those at Time 1, the cardiac function levels at Time 1 and Time 2 are higher than those at Time 0, and the levels at Time 2 exceed those at Time 1. So, the serum lipids and inflammatory indicators levels in the OG are below those in the CG (P<0.05), but the cardiac function levels are higher. The results showed that the levels among groups, time, and interaction is significant (P<0.05). Clopidogrel combined with Atorvastatin can effectively reduce the serum lipid levels and inflammatory factors in patients, which is conducive to improving the cardiac function of patients.

INTRODUCTION

Angina pectoris and coronary heart disease (APCH) is a cardiovascular disease with high incidence rate. After onset, the patient presents with symptoms such as shortness of breath, chest tightness, and angina pectoris. In addition, the disease is progressing rapidly. If the patient is not treated effectively in a timely manner, it is highly likely to develop into diseases such as myocardial infarction and arrhythmia, posing a serious threat to the patient's life, work, and even life safety. The occurrence of APCH disease is related to the abnormal function of the coronary artery, the blood supply vessel of the heart. When atherosclerosis or unstable plaque ruptures, it is easy to cause abnormal changes in myocardial blood supply, and then induce the disease (Qi-Dong *et al*., 2022). Combined with the pathogenesis, the main purpose of treating this disease is to improve coronary artery function and restore normal blood supply to the myocardium. Percutaneous coronary intervention is the main clinical treatment method for this disease. Implantation of vascular stents and mechanical thrombectomy can effectively restore vascular patency and myocardial blood supply, with significant clinical therapeutic effects (Zhang and Chang, 2019). However, relevant studies have pointed out that dyslipidemia and coagulation dysfunction are the main causes of coronary heart disease. After effectively unblocking the coronary arteries, if effective anticoagulation and lipid-lowering interventions are not carried out, the risk of re-blockage is relatively high (Martikainen *et al*., 2021). Atorvastatin is a widely used lipid-lowering drug in clinic. Cholesterol synthase is inhibited to reduce LDL-C level, which can delay the progress of coronary atherosclerosis (Akbar *et al*., 2021). As an antiplatelet drug, clopidogrel prevents

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coronary artery thrombosis by inhibiting platelet aggregation and thrombosis (Liu *et al*., 2021). The two drugs have a significant synergistic effect in reducing coronary artery thrombosis. Previously, it was mainly used for the prevention of restenosis after coronary intervention surgery. The clinical treatment effect has been widely recognized. When angina pectoris coronary heart disease does not develop to the myocardial infarction, most patients are unwilling to undergo interventional surgery. Treatment methods such as lowering blood lipids and anticoagulation can also achieve certain therapeutic effects, delaying disease progression. Therefore, the regulatory effect of clopidogrel combined with atorvastatin on LDL-C, TG and TC in patients with APCH disease is analyzed in detail.

MATERIALS AND METHODS

General data

The research subjects are selected from patients with APCH disease admitted from January 2021 to December 2022. The research is conducted after approval by the ethics committee. The inclusion amount of the research object is calculated by the Akkaif *et al*. (2021), among them, probability value p=0.5, error value α= 0.05, statistic Z=1.96, total E=107. The calculation results show that 83 patients need to be included in this research. Patients are randomly numbered 1-83. Patients with odd numbers (42 cases) and even numbers (41 cases) are included in the control group (CG) and the observation group (OG), respectively. The general information between groups (P>0.05) has grouping comparison value. Table I illustrates the specific information.

Inclusion and exclusion criteria

Inclusion criteria: (a) Patients meet the relevant diagnostic criteria for coronary heart disease in the "Expert Consensus on Stable Coronary Heart Disease Rehabilitation Drug Prescription Management (2016 Edition)" (Ping-ping *et al*., 2022). (ii) The patient is diagnosed through clear coronary CTA/coronary angiography examination. (iii) The patient is conscious and has the ability to cooperate with research and investigation. (iv) The patient has informed consent to the content of this research. Exclusion criteria: (i) Patients with acute myocardial infarction, heart valve disease, or concomitant other heart diseases. (ii) Patients with a history of combined cardiac stenting or other surgical treatments. (iii) Patients with drug intolerance treated in the research. (iv) Patients with a history of trauma or surgery within 3 months. (v) Patients with malignant tumor and infectious diseases.

Research methods

All patients receive basic treatment for coronary heart disease after enrollment, including bed rest, oxygen inhalation, sedation, etc.

Control group (CG) received subcutaneous injection of low molecular weight heparin sodium injection (Alfa Weisman Pharmaceuticals, Italy, imported drug registration number H20140281, specification: 0.6ml) 4100IU, once every 12 h, continuously administered for 7 days as a treatment course. Oral aspirin enteric coated tablets (Linfen Baozhu Pharmaceutical Co., Ltd., national drug approval number H14023070, specification: 25mg) 25mg/time, once a day, continuous medication for 7 days as one treatment course. The patient receives 4 weeks of the treatment.

Observation group (OG) received oral Clopidogrel (Shenzhen Salubris Pharmaceuticals Pharmaceutical Co., Ltd., GYZZ H20000542, specification: 25mg) 75mg/time orally, once a day after dinner. Oral Atorvastatin (Beijing Jialin Pharmaceutical Co., Ltd., GYZZ H19990258, specification: 20mg) 20mg/time, once a day after dinner. The patient receives 4 weeks of the treatment.

Observed indicators

Serum lipid level 3ml of fasting elbow vein blood is collected from patients at Time 0, Time 1, and Time 2. After centrifugation (speed: 3200r/min, centrifugation radius: 10cm), serum is obtained and stored at -20□ for testing. The patient's serum lipid levels are measured using a dual reagent enzyme method. The detection contents include LDL-C (reference range: 1.53-3.45mmol/L), TG (reference range: 0.56-1.7mmol/L), and TC (reference range: 2.83-5.20mmol/L).

Table I. General data of patients ($\bar{x}$±s, n(%)).

Group	Gender		Age (years)	Types of angina pectoris		BMI (g/m²)
	Male	Female		Unstable type	Labor type	
CG (n=42)	26(61.90)	16(38.10)	65.07±10.66	31(73.81)	11(26.19)	25.21±2.36
OG (n=41)	29(70.73)	12(29.27)	65.10±10.39	32(78.05)	9(21.95)	24.99±2.53
t/X²	0.723		0.011	0.203		0.410

P	0.395	0.991	0.652	0.683

BMI, body mass index.

The blood pressure samples are collected and treated in the same way as above. The inflammatory factors in patients are measured by enzyme-linked immunosorbent assay. The detection contents include Interleukin 6 (IL-6), hypersensitive C-reactive protein (hs-CRP).

Cardiac function Doppler color ultrasound was used to detect the cardiac function of the two groups. The detection time is the same as above. The detection contents include cardiac minute output (CO), cardiac index (CI), and ejection fraction (EF).

To ensure the accuracy and scientificity of the research data, a cardiologist who is not involved in this study is invited to be responsible for data collection. During the process, the physician is unaware of the patient grouping situation.

Statistical methods

The statistical software SPSS 26.0 is used to process data. The measurement data conforming to the normal distribution is represented as $\bar{x}\pm s$. The independent sample *t*-test and paired *t*-test are adopted for inter group and intra group comparison. The counting data is presented in the form of [n(%)] and subjected to x^2 test. $P<0.05$ represents statistically significant.

RESULTS

Table I shows general information comparison of the patients included in the study. As the table shows, there are no significant differences between the CG and the OG so it can be concluded that they are homogenous groups.

Comparison results of serum lipid, inflammatory factor and cardiac function levels between groups, time, and interaction (P<0.05) are depicted in Table II. As shown the table, there is no distinctions ($P>0.05$) in the serum lipid levels at Time 0 between groups. The levels at Time 1 and Time 2 are lower than Time 0, while the levels at Time 2 are lower than Time 1. The level of the OG is lower than the CG ($P<0.05$). After the treatment, the patient's serum lipid levels show a decreasing trend. They have no difference in inflammatory factors at Time 0 ($P>0.05$). The levels at Time 1 and Time 2 are lower than Time 0, while the levels at Time 2 are lower than Time 1. The inflammatory factor in the OG is below the CG ($P<0.05$). Inflammatory factors have statistical significance in group, time, and interaction ($P<0.05$). After the treatment, the levels of inflammatory indicators in patients show a decreasing trend (Table II). There is no significant distinction in cardiac function levels between groups at Time 0 ($P>0.05$). The levels at Time 1 and Time 2 exceed those at Time 0, while the levels at Time 2 are higher than those at Time 1. At the same time point, the level of the OG exceeds the CG ($P<0.05$).

Table II. Serum lipid, inflammatory factor and cardiac function levels in study groups (Mean±SD).

Indicators		CG (n=42)	OG (n=41)	t	P
LDL-C (mmol/L)	Time 0	3.33±0.41	3.35±0.43	0.217	0.829
	Time 1	2.51±0.28	2.31±0.31	3.086	0.003
	Time 2	2.06±0.32	1.71±0.36	4.684	<0.001
TG (mmol/L)	Time 0	3.35±0.41	3.36±0.42	0.110	0.913
	Time 1	2.72±0.19	2.41±0.20	7.241	<0.001
	Time 2	2.53±0.21	2.11±0.19	9.547	<0.001
TC (mmol/L)	Time 0	4.18±1.20	4.29±0.93	0.466	0.642
	Time 1	3.01±0.41	2.61±0.34	4.832	<0.001
	Time 2	2.52±0.33	2.13±0.34	5.303	<0.001
IL-6 (ng/L)	Time 0	1.08±0.21	1.07±0.26	0.193	0.847
	Time 1	0.78±0.13	0.56±0.11	8.313	<0.001
	Time 2	0.63±0.08	0.41±0.07	13.320	<0.001
hs-CRP (ng/L)	Time 0	15.21±2.62	15.34±2.48	0.232	0.817
	Time 1	11.65±1.75	9.52±1.86	5.375	<0.001
	Time 2	8.36±1.54	5.28±1.36	9.649	<0.001
CO (L/min)	Time 0	2.83±0.81	2.82±0.84	0.055	0.956
	Time 1	3.41±1.01	3.91±0.92	2.356	0.021
	Time 2	3.79±1.25	4.65±1.15	3.260	0.002
CI [L/(min·m²)]	Time 0	1.62±0.41	1.63±0.44	0.107	0.915
	Time 1	2.28±0.44	2.68±0.41	4.282	<0.001
	Time 2	3.02±0.43	3.58±0.52	5.352	<0.001
EF (%)	Time 0	36.25±4.13	35.95±4.81	0.305	0.761
	Time 1	46.52±7.96	50.69±6.32	2.639	0.010
	Time 2	55.42±8.12	63.52±8.42	4.462	<0.001

LDL-C: $F_{Between}/F_{Time}/F_{Inter}$= 52.656/ 5942.131/ 8.686, $P_{Between}/P_{Time}/P_{Inter}$= <0.001/ <0.001/ <0.001. TG: $F_{Between}/F_{Time}/F_{Inter}$= 147.374/9465.977/ 20.326, $P_{Between}/P_{Time}/P_{Inter}$= < 0.001/ < 0.001/ < 0.001. TC: $F_{Between}/F_{Time}/F_{Inter}$= 23.402/ 2506.936/ 5.279, $P_{Between}/P_{Time}/P_{Inter}$= < 0.001/ <0.001/ <0.001. IL-6: $F_{Between}/F_{Time}/F_{Inter}$= 189.671/ 2959.154/ 21.672, $P_{Between}/P_{Time}/P_{Inter}$= <0.001/ <0.001/ <0.001. hs-CRP: $F_{Between}/F_{Time}/F_{Inter}$= 154.645/ 3991.319/ 22.737, $P_{Between}/P_{Time}/P_{Inter}$= <0.001/ <0.001/ <0.001. CO: $F_{Between}/F_{Time}/F_{Inter}$= 42.444/ 1308.580/ 6.219, $P_{Between}/P_{Time}/P_{Inter}$= <0.001/ <0.001/ <0.001. CI: $F_{Between}/F_{Time}/F_{Inter}$= 113.648/ 3847.453/ 14.402, $P_{Between}/P_{Time}/P_{Inter}$= < 0.001/ <0.001/ <0.001. EF: $F_{Between}/F_{Time}/F_{Inter}$= 72.768/ 5432.818/ 12.003, $P_{Between}/P_{Time}/P_{Inter}$= <0.001/ <0.001/ <0.001.

DISCUSSION

In recent years, with the progress of living standards and the increase of work pressure, the incidence rate of cardiovascular diseases is gradually increasing. Angina pectoris coronary heart disease is one of the common

cardiovascular diseases. Abnormal coagulation function, atherosclerosis, elevated blood lipid level, and local plaque inflammation are the important pathological basis of the disease. When abnormal coronary artery function occurs, it may cause obstruction of local blood supply to the myocardium, inducing to the disease (Liu *et al*., 2022). Relevant studies have pointed out that dyslipidemia is crucial in the pathogenesis of angina and coronary heart disease (Hu *et al*., 2022; Zhao *et al*., 2021). First, the accumulation of lipids in the blood vessels is a major prerequisite for atherosclerosis. Atherosclerotic plaques can lead to narrowing of the lumen, which will induce to the blood supply obstruction to the corresponding tissues. Secondly, elevated blood lipids can lead to an increase in blood viscosity and blood flow resistance. Stimulated by external factors such as emotional fluctuations and fatigue, turbulence can form in the local area of the coronary artery, leading to impaired blood supply to the myocardium and triggering symptoms of myocardial ischemia. Therefore, reducing blood lipid levels and anticoagulants play an irreplaceable role in the treatment of APCH.

Elevated blood lipid levels are considered an independent risk factor for APCH. Among them, high levels of TG can increase blood viscosity, affect blood flow, and increase the risk of thrombosis. In addition, TG can induce coronary heart disease through diabetes, insulin resistance and other pathways (Li *et al*., 2020). TC mainly refers to the sum of various cholesterol components (LDL-C, HDL-C) in the blood. High levels of TC are usually associated with high LDL-C and low HDL-C. This is one of the factors that can cause coronary heart disease (Ha *et al*., 2020). Elevated LDL-C levels are one of the important links in the onset of angina and coronary heart disease, which can induce diseases through various mechanisms. Firstly, LDL-C carries cholesterol in the blood to the vascular wall and permeates into the intimal layer. In the inner membrane, LDL-C is taken up and enters macrophages to form cholesterol foam cell. These cholesterol foam cell gradually accumulate and form plaques. Secondly, the plaques accumulated by LDL-C may become unstable and prone to rupture or ulceration. When a plaque ruptures, coagulation factors in the blood come into contact with tissue factors within the plaque, forming a thrombus. Furthermore, LDL-C can be oxidized within the plaque, forming oxidized low-density lipoprotein (ox-LDL). ox-LDL can activate endothelial cells and macrophages, release inflammatory mediators, and attract more inflammatory cells to infiltrate plaque areas (Cai *et al*., 2023; Podadera-Herreros *et al*., 2022). The regulatory effect of clopidogrel combined with atorvastatin on LDL-C, TG and TC in patients with APCH is analyzed in detail. From the experimental results, after therapy, the LDL-C, TG, and TC in the OG are lower than those in the CG. This is consistent with the research results of domestic scholars such as Petrelli *et al*. (2022). Atorvastatin and clopidogrel have significant effects on regulating blood lipids in patients with APCH. There is a high consistency. Atorvastatin is a statin drug, which has obvious inhibitory effect on the physiological function of cholesterol synthase (HMG-CoA reductase). This reduces cholesterol synthesis within liver cells, increases LDL receptors on the surface of liver cells, thereby increasing LDL-C and lowering plasma LDL-C levels (Zhao *et al*., 2023). Clopidogrel is a widely used antiplatelet drug. By inhibiting the activation of ADP receptor P2Y12 in platelets and blocking the ADP signaling pathway, platelet aggregation and thrombosis formation are reduced. This can effectively prevent thrombosis, maintain vascular patency, and reduce myocardial ischemia caused by coronary artery thrombosis (Kumar *et al*., 2020).

LDL-C is involved in inflammatory factors in the process of inducing angina and coronary heart disease. IL-6 is involved in the formation and stability of plaques. The increase of IL-6 level can promote endothelial cell injury and activation, and stimulate monocyte and macrophages to release inflammatory mediators. It can exacerbate inflammation within plaques, increase plaque instability, and thus increase the risk of myocardial ischemia and myocardial infarction (Dandare *et al*., 2023). Hs-CRP also has a certain regulatory effect on plate stability. Therefore, attention should be paid to controlling the patient's inflammatory factors during the treatment process. According to the research results, after the treatment, the IL-6 and hs-CRP in the OG exceed the CG. Relevant studies indicate that clopidogrel and atorvastatin have certain anti-inflammatory effects. It reduces plaque inflammation by inhibiting inflammatory mediators and cell adhesion molecules, thus reducing the progress of angina pectoris and coronary artery disease (Kadry *et al*., 2021; Xia *et al*., 2022). Under the premise of ideal lipid regulation and inflammation control, the risk of patient progression can be avoided, which is beneficial for improving the patient's heart function level. The research results show that the CO, CI, and EF levels in the OG exceed those in the CG after the treatment. It further suggests that clopidogrel combined with atorvastatin has a higher application value in patients with APCH.

CONCLUSION

Clopidogrel combined with atorvastatin can effectively reduce the blood lipids and inflammatory factors in patients with APCH. Rupture of atherosclerotic plaque can delay the risk of disease progression. It can

reduce the incidence of coronary artery restenosis and cardiovascular events, which is beneficial for improving the prognosis of patients.

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IRB approval

This study was approved by the Dongyang People's Hospital, Jinhua, China.

Ethical approval

The study was carried out in compliance with guidelines issued by ethical review board committee of Dongyang People's Hospital, China. The official letter would be available on fair request to corresponding author.

Statement of conflict of interest

The authors have declared no conflict of interest.

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