

Effect of Ezetimibe combined with Simvastatin in the treatment of coronary heart disease: a retrospective analysis

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Abstract. – OBJECTIVE: The aim of this study was to explore the effect of Ezetimibe combined with Simvastatin in the treatment of coronary heart disease (CHD).

PATIENTS AND METHODS: Clinical data of 101 patients with CHD, admitted to our hospital from February 2022 to May 2023, were retrospectively analyzed. Among them, 49 patients received Simvastatin (Simvastatin group), and 52 patients received Simvastatin+Ezetimibe (Simvastatin+Ezetimibe group). Levels of blood lipid indicators, inflammatory factors, cardiac function indicators, and incidences of major adverse cardiovascular events (MACE) between the two groups were compared before and after the treatment.

RESULTS: After the treatment, high-density lipoprotein cholesterol (HDL-C), cardiac index (CI), and left ventricular ejection fraction (LVEF) in both groups were higher than those before the treatment, and overall higher in the Simvastatin+Ezetimibe group. Levels of low-density lipoprotein-cholesterol (LDL-C), triglycerides (TG), total cholesterol (TC), monocyte chemoattractant protein-1 (MCP-1), chemokine ligand 19 (CCL19), high sensitivity C-reactive protein (hs-CRP), cardiac output (CO) in the two groups were lower than before the treatment. These indexes were significantly lower in the Simvastatin+Ezetimibe group ($p<0.05$) compared to the Simvastatin group. During the treatment, the incidence of MACE in the Simvastatin+Ezetimibe group (3.85%) was significantly lower than that in the Simvastatin group (16.33%) ($p<0.05$).

CONCLUSIONS: Compared with Simvastatin alone, a combination of Ezetimibe and Simvastatin can more effectively regulate the level of blood lipids, reduce the inflammatory reaction in the body, improve heart function, and lower the risk of MACE.

Key Words:

Ezetimibe, Simvastatin, Coronary heart disease.

Introduction

Coronary heart disease (CHD) is an important cause of mortality, and significantly impacts the quality of life of patients^{1,2}. Research^{3,4} has found that atherosclerosis is an important pathogenic factor of CHD, and abnormal lipid metabolism is closely related to the formation and progress of atherosclerosis. Therefore, lipid-lowering therapy is an important intervention measure for CHD. Simvastatin is a commonly used lipid-lowering drug from the statin family. It can efficiently inhibit the development and progression of atherosclerosis⁵. However, the overall effect of Simvastatin alone is poor, and increasing the medication dosage will increase the risk of adverse reactions such as elevated liver enzymes^{5,6}. Ezetimibe is a new nonstatin lipid-lowering drug, which can block the exogenous absorption pathway of cholesterol⁷. The combination of these agents can improve blood lipid levels through both exogenous and endogenous pathways of cholesterol metabolism, exerting strong lipid-lowering effects^{7,8}.

In the recent two years, our hospital has treated CHD patients using a combination of Simvastatin and Ezetimibe. The aim of this study is to review and analyze the clinical data of these patients before and after the treatment, in the hope of providing a practical reference basis for clinical treatment of CHD.

Patients and Methods

Patients

Clinical data of 101 CHD patients (56 males and 45 females), admitted to our hospital from February 2022 to May 2023, were included. The age of the patients ranged from 41 to 82 years, with an

average age of 63.6±9.2 years. Of them, 49 patients received the Simvastatin treatment and were set as the Simvastatin group, and 52 patients were treated with Simvastatin+Ezetimibe, and were set as the Simvastatin+Ezetimibe group. The Ethics Committee of Cangzhou Central Hospital approved this study with the number 2023-168-01 (Y).

Inclusion criteria

- Meet the diagnostic criteria for CHD⁹.
- Receive Simvastatin or Simvastatin+Ezetimibe treatment.
- Complete treatment for more than 4 weeks.
- Complete clinical data.
- Age >18 years old.

Exclusion criteria

- Women during lactation and pregnancy.
- Existence of organic lesions such as kidney and liver.
- Individuals with rheumatic diseases.
- Individuals with malignant tumors.
- Individuals with heart failure or valvular heart disease.
- Patients who have previously undergone coronary artery surgery and interventional therapy.

Drug Therapy

Simvastatin-(Shandong Luoxin Pharmaceutical Group Co., Ltd.: Approval No.: H20065119; specification: 10 mg/tablet), oral 20 mg/time, once a day.

Ezetimibe-(MSD International GmbH, Singapore Branch; Approval No.: H20130837; specification: 10 mg), orally 10 mg/time, once a day.

The following indicators were collected before and after the treatment: 1) Lipid indicators, including high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and total cholesterol (TC) levels. After fasting for 10 hours, 5 ml of elbow vein blood was drawn on an empty stomach the next morning; the Roche Cobas 8000 fully automatic biochemical analyzer (Basel, Switzerland) was used to detect the above indicators. 2) Inflammatory factors, including the levels of monocyte chemoattractant protein-1 (MCP-1), chemokine ligand 19 (CCL19), and high sensitivity C-reactive protein (hs-CRP). Two sets of blood samples were extracted, centrifuged, and the levels of the above indicators were determined by enzyme-linked immunosorbent assay. The reagent kit was purchased from Shanghai Enzyme-linked Biotechnology Co., Ltd. (Shang-

hai, China) 3) Cardiac function indicators, including cardiac index (CI), Left ventricular ejection fraction (LVEF), and cardiac output (CO). Using Philip siE33 color Doppler ultrasound diagnostic instrument (Amsterdam, Netherlands), the probe frequency was 1-5 MHz. The patient was positioned on the left side, breathing calmly. LVEF and CO in the two-dimensional conventional mode of echocardiography were measured. 4) Incidence rate of cardiac major cardiovascular adverse events (MACE), including unstable angina, death during consensual sex, and myocardial infarction.

Statistical Analysis

All data analysis was conducted using SPSS 22.0 software (IBM Corp., Armonk, NY, USA). The normality of the data was evaluated using the Shapiro-Wilk test. The data of normal distribution were expressed by mean ± standard deviation, and *t*-test was used. Data of non-normal distribution were expressed by median and interquartile interval, and the Mann-Whitney U test was used. The counting data was represented by the number of use cases, and the Chi-square test was used. *p*<0.05 was considered statistically significant.

Results

A total of 101 patients were included in this retrospective study, including 52 patients in the Simvastatin+Ezetimibe group and 49 patients in the Simvastatin group. There was no statistically significant difference in baseline data between the two groups of patients (*p*>0.05) (Table I).

There was no significant difference in blood lipid levels between the two groups before the treatment (*p*>0.05). After the treatment, HDL-C was higher in the two groups than before the treatment, and higher in the Simvastatin+Ezetimibe group compared to the Simvastatin group. Levels of LDL-C, TG, and TC were lower than before the treatment, and lower in the Simvastatin+Ezetimibe group compared to the Simvastatin one (*p*<0.05) (Table II).

There was no significant difference in the levels of inflammatory factors between the two groups before the treatment (*p*>0.05). After the treatment, the levels of serum MCP-1, CCL19, and hs-CRP in the two groups decreased compared to those before the treatment. Simvastatin+Ezetimibe treatment was associated with significantly lower MCP-1, CCL19, and hs CRP than the Simvastatin treatment alone (*p*<0.05) (Table III).

Table I. Comparison of two groups of baseline data.

Baseline information	Simvastatin+Ezetimibe group (n=52)	Simvastatin group (n=49)	χ^2/t	<i>p</i>
Gender (Male/Female)	31/21	25/24	0.754	0.385
Age (Years)	64.2±8.9	62.8±9.5	0.763	0.447
Diabetes (Yes)	10 (19.2)	14 (28.6)	1.215	0.270
Hypertension (Yes)	17 (32.7)	18 (36.7)	2.504	0.286
Smoke (Yes)	23 (44.2)	17 (34.7)	0.959	0.327

Table II. Comparison of blood lipid index levels between two groups (mmol/L).

Time	Group	HDL-C	LDL-C	TG	TC
Before treatment	Simvastatin+Ezetimibe group (n=52)	1.20±0.30	3.70±0.90	4.12±0.96	5.44±0.83
	Simvastatin group (n=49)	1.26±0.35	3.59±1.01	4.01±1.00	5.62±0.98
	<i>t</i>	-0.844	0.612	0.567	-0.964
	<i>p</i>	0.401	0.542	0.572	0.337
After treatment	Simvastatin+Ezetimibe group (n=52)	1.90±0.37	1.83±0.64	2.8 (2.2, 3.3)	2.9 (2.25, 3.6)
	Simvastatin group (n=49)	1.53±0.44	2.48±0.78	3.2 (2.8, 4.0)	3.7 (3.1, 4.0)
	<i>t/Z</i>	4.578	-4.554	-3.445	-4.219
	<i>p</i>	<0.001	<0.001	0.001	<0.001

High-density lipoprotein cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), triglycerides (TG), total cholesterol (TC).

Table III. Comparison of two groups of inflammatory factors.

Time	Group	MCP-1 (ng/L)	CCL19 (ng/L)	hs-CRP (mg/L)
Before treatment	Simvastatin+Ezetimibe group (n=52)	154 (134.5, 165)	83.9±9.7	36.9±7.9
	Simvastatin group (n=49)	158 (132, 174)	82.5±10.5	37.8±8.4
	<i>t/Z</i>	-0.708	0.692	-0.538
	<i>p</i>	0.479	0.490	0.592
After treatment	Simvastatin+Ezetimibe group (n=52)	82 (68, 89)	60.0±7.8	9.5 (9, 13.5)
	Simvastatin group (n=49)	107 (84, 121)	68.1±8.8	14 (10, 18)
	<i>t/Z</i>	-5.551	-4.924	-3.866
	<i>p</i>	<0.001	<0.001	<0.001

Monocyte chemoattractant protein-1 (MCP-1), chemokine ligand 19 (CCL19), high sensitivity C-reactive protein (hs-CRP).

There was no significant difference in cardiac function between the two groups before the treatment ($p>0.05$). After the treatment, CI and LVEF in both groups were higher than those before the treatment. Simvastatin+Ezetimibe resulted in higher CI and LVEF compared to Simvastatin alone. CO in the two groups was lower than that before the treatment, and markedly lower in the Simvastatin+Ezetimibe group compared to the Simvastatin group ($p<0.05$) (Table IV).

The incidence of MACE in the Simvastatin+Ezetimibe group (3.85%) was significantly lower than that in the Simvastatin group (16.33%) ($p<0.05$) (Table V).

Discussion

The results of this study show that the combined treatment with Simvastatin+Ezetimibe has higher application value in the treatment of CHD patients than compared with Simvastatin alone, and has significant advantages in regulating blood lipid levels and improving patients' cardiac function. We suggest that this difference is related to the mechanism of action of these two agents. Simvastatin is a typical statin preparation⁶. It mainly inhibits 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) to reduce cholesterol synthesis and achieve lipid-lowering effects¹⁰. However, about

Table IV. Comparison of cardiac function between two groups.

Time	Group	CI (L/min/m ²)	LVEF (%)	CO (L/min)
Before treatment	Simvastatin+Ezetimibe group (n=52)	2.53±0.49	57 (52.5, 64.5)	2.65 (2.4, 3.0)
	Simvastatin group (n=49)	2.62±0.46	60 (57, 63)	2.8 (2.5, 3.2)
	<i>t/Z</i>	-1.014	-1.644	-1.149
	<i>p</i>	0.312	0.100	0.250
After treatment	Simvastatin+Ezetimibe group (n=52)	3.94±0.56	77 (73, 82)	5.71±0.54
	Simvastatin group (n=49)	3.39±0.52	71 (68, 73)	4.95±0.61
	<i>t/Z</i>	5.180	-5.369	6.651
	<i>p</i>	<0.001	<0.001	<0.001

Cardiac index (CI), left ventricular ejection fraction (LVEF), cardiac output (CO).

Table V. Comparison of MACE incidence rates between two groups.

Group	Unstable angina pectoris	Sudden cardiac death	Myocardial infarct	Total occurrence rate
Simvastatin+Ezetimibe group (n=52)	1 (1.92)	0 (0.00)	1 (1.92)	2 (3.85)
Simvastatin group (n=49)	4 (8.16)	1 (2.04)	3 (6.12)	8 (16.33)
χ^2				4.405
<i>p</i>				0.036

Major adverse cardiovascular events (MACE).

40% to 50% of cholesterol is excreted with bile daily^{6,10}. Ezetimibe is a selective cholesterol absorption inhibitor, which can bind to C1 proteins in the brush border of small intestinal epithelial cells^{8,11}. Thus, it prevents intestinal epithelial cells from absorbing bile and dietary cholesterol and reduces cholesterol transport from the intestine to the liver¹¹, improving the clearance rate of cholesterol in the blood and exerting the lipid-lowering effect^{11,12}. Ezetimibe and Simvastatin have different mechanisms of action, and, when combined, can more efficiently inhibit the absorption and synthesis of cholesterol by the body through complementary action^{10,13}. Ouchi et al¹⁴ confirmed that Ezetimibe can effectively regulate blood lipid levels of patients with cardiovascular disease, which is conducive to improving the heart function of patients. These observations are consistent with the results of our study. At the same time, even in the absence of treatment with statins, the level of TC and LDL-C can be significantly reduced by Ezetimibe alone¹⁵. Musunuru¹⁶ confirmed that Ezetimibe has significant advantages in regulating blood lipid metabolism and restoring heart function in patients with coronary artery disease. Ezetimibe is an intestinal Niemann-Pick C1-like1 (NPC1L1) receptor antagonist, which can inhibit

the absorption of cholesterol in the intestine and can reduce LDL-C levels by 15-20% in patients with hypercholesterolemia^{15,16}. Rubino et al¹⁷ confirmed the clinical value of the combined treatment scheme of statin preparation and Ezetimibe and pointed out that the combination of Ezetimibe and statins is not subject to cytochrome P450 (CYP450) restrictions. Therefore, there won't be adverse effects on the mechanism of action of atorvastatin, and can effectively inhibit the exogenous absorption channel of cholesterol¹⁷. The combination of the two can also have an inhibitory effect on intestinal absorption, prevent the synthesis of cholesterol by the liver, and further enhance the lipid-lowering effect by downregulating TC levels^{15,16}.

The inflammatory response also plays an important role in the pathogenesis and progression of CHD. Studies¹⁸ have shown that there is a significant accumulation of lipids under the endothelium of blood vessels, which can generate a large number of inflammatory cells and cause the aggregation of inflammatory mediators through the waterfall effects factor, resulting in the production of new vitamin-like substances. Fibrous plaques are formed as the disease progresses, and inflammatory factors may promote

a decrease in the stability of these plaques and an increased risk of thrombosis¹⁹. CCL19 can activate humoral immunity, promote the exudation of inflammatory factors, and objectively reflects arterial injury²⁰. Hs-CRP is an acute-phase responsive protein that is closely related to the degree of inflammatory response in coronary artery disease²¹. MCP-1 can activate many inflammatory factors in the form of paracrine/autocrine signaling, plays an important role in unstable plaque formation, and can regulate the pathogenesis of CHD²². Our study found that the levels of MCP-1, CCL19, and hs-CRP in the Simvastatin+Ezetimibe group were lower than those in the Simvastatin group after the treatment, suggesting that Ezetimibe combined with Simvastatin can also reduce the degree of inflammatory reaction in CHD patients. Seenak et al²³ also confirmed that Ezetimibe and statins could effectively inhibit the degree of the inflammatory stress response, which is consistent with the conclusions of our study. We may speculate that Ezetimibe and Simvastatin not only have the effect of reducing lipid levels, but also can reduce the levels of inflammatory factors, improve the stability of plaque, and play an overall anti-inflammatory role^{17,23}. The results of our study also showed that the incidence of MACE in the Simvastatin+Ezetimibe group was lower than that in the Simvastatin group, indicating that Ezetimibe combined with Simvastatin could also improve the prognosis of CHD patients¹². It is possible that as this combined medication regimen more effectively regulates blood lipid levels and reduces the degree of inflammatory response²⁴, it also effectively reduces the occurrence of MACE and ensures a good outcome of the disease^{12,24}.

Limitations

This is a single-center retrospective study with small sample size and selection bias. Further multi-center, large-sample randomized controlled trials are needed to verify the effect of the combined Simvastatin+Ezetimibe regimen in the treatment of CHD and its long-term impact.

Conclusions

Compared with Simvastatin alone, Ezetimibe+Simvastatin combination can more effectively regulate the level of blood lipids, reduce the inflammatory reaction, more efficiently improve heart function, and lower the risk of MACE.

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Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' Contributions

BL conceived and designed the study. YL, WP and YL collected the data and performed the analysis. BL was involved in the writing of the manuscript. ZX and JW edited the manuscript. All authors have read and approved the final manuscript.

Ethics Approval

The Ethics Committee of Cangzhou Central Hospital approved this study with the number 2023-168-01 (Y).

Informed Consent

Written informed consent was obtained from the patient or legal guardian.

Conflict of Interest

The authors declare that they have no competing interests.

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