THE EFFICACY OF COENZYME Q₁₀ IN COMBINATION WITH ATORVASTATIN ON CORONARY HEART DISEASE

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Manuscript received: December 2019

Abstract

The aim of this study was to evaluate the efficacy of coenzyme Q₁₀ (CoQ₁₀) in combination with atorvastatin on coronary heart disease (CHD). In this study there were included 84 patients with CHD and divided into two groups, a control group (42 patients), treated with atorvastatin and an experimental group (42 patients) that received atorvastatin and CoQ₁₀. CoQ₁₀ levels, transaminase activities (ALT and AST), blood lipid, cardiac function, and hemodynamic, were measured and evaluated before the treatment and 3 months after the treatment. Both treatments were safe and effective in the clinical management if lipidic imbalance in CHD, but the experimental group had better therapeutic effects. The CoQ₁₀ level in the experimental group increased after the treatment ($p < 0.05$), while in the control group decreased significantly ($p < 0.05$). ALT and AST levels did not changed significantly after the treatment in the experimental group, while in the control group, it was observed a significant increase ($p < 0.05$). After treatment, the left ventricular diastolic function of the experimental group was improved significantly ($p < 0.05$). Meanwhile, the left ventricular diastolic function of the control group was also improved to some extent, but the difference was not statistically significant ($p > 0.05$). In conclusion, CoQ₁₀ supplementation could avoid the increase of transaminases caused by atorvastatin, and could enhance the lipid-lowering effect of atorvastatin and improve the cardiac function effectively.

Rezumat

Scopul acestui studiu a fost evaluarea eficacității coenzimei Q₁₀ (CoQ₁₀) în combinație cu atorvastatina în bolile coronariene (CHD). Au fost incluși 84 de pacienți cu CHD, împărțiți în două grupuri, control (42 de pacienți), grupul tratat cu atorvastatină și un grup experimental (42 de pacienți) care a primit atorvastatină și CoQ₁₀. Nivelurile CoQ₁₀, activitatea transaminazelor (ALT și AST), a lipidelor plasmatiche, funcția cardiacă și hemodinamica au fost evaluate înainte de tratament și după 3 luni. Ambele terapii au fost sigure și eficiente în managementul clinic al dezechilibrului lipidic în CHD, dar grupul experimental a prezentat efecte terapeutice superioare. Nivelul CoQ₁₀ în grupul experimental a crescut după tratament ($p < 0,05$), în timp ce în grupul martor a scăzut semnificativ ($p < 0,05$). Nivelurile ALT și AST nu s-au modificat semnificativ după tratament în grupul experimental, în timp ce în grupul martor s-a observat o creștere semnificativă ($p < 0,05$). După tratament, funcția diastolică a ventriculului stâng în grupul experimental a fost îmbunătățită. Funcția diastolică a ventriculului stâng în grupul martor a fost, de asemenea, îmbunătățită. În concluzie, suplimentarea cu CoQ₁₀ ar putea evita creșterea transaminazelor în terapia cu atorvastatină, și ar putea îmbunătăți profilul lipidic și funcția cardiacă.

Keywords: coronary heart disease, coenzyme Q₁₀, atorvastatin, blood lipids

Introduction

Coronary heart disease (CHD) is the most common type of disease in the corresponding arterial blood supply organs caused by atherosclerosis [1]. In recent years, with the widespread use of statins, clinical studies have focused on the correlation between statins and coenzyme Q₁₀ (CoQ₁₀). By inhibiting the activity of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, statins reduce not only the intracellular cholesterol synthesis but also of some intermediate related to cholesterol synthesis, including the mevalonic acid (MVA). MVA is necessary for CoQ₁₀ synthesis and a decrease of MVA will lead to the unavailability of CoQ₁₀ production [2-4]. CoQ₁₀ is an endogenous cofactor, whose major function is to participate in the electron transfer on the mitochondrial respiratory

chain. It also has the functions of scavenging oxygen free radicals, stabilizing cell membranes, and prevent lipid peroxidation [5, 6]. Theoretically, while inhibiting cholesterol synthesis, statins also cause a decrease in CoQ₁₀ levels *in vivo* [7], leading to a dysfunction of the respiratory chain of the mitochondria in the cells. Eventually, it causes side effects in patients, such as myalgia, sarcopenia and liver damage [8, 9]. However, whether CoQ₁₀ has a protective effect on another statins-induced side effect, i.e., liver damage dominated by elevated transaminases activity, and whether CoQ₁₀ supplementation impacts the lipid-lowering effects of statins, are seldom reported. In this study, the effects of atorvastatin on CoQ₁₀ levels in CHD patients and the reversal effect of oral CoQ₁₀ were investigated in order to explore the possibility of the beneficial co-administration in the treatment of CHD.

Materials and Methods

Patients

Eighty-four CHD patients aged between 42 and 73 years, treated from July 2018 to September 2019 in the Affiliated Hongqi Hospital of Mudanjiang Medical University, China, were included in the study. The patients were randomly divided into an experimental group (42 cases) and a control group (42 cases). Before the experiment, the age, gender, height, body mass index (BMI), blood pressure, history of smoking, family disease history, history of diabetes mellitus, and carotid artery plaque of each patient were recorded. The Ethics Committee of Affiliated Hongqi Hospital of Mudanjiang Medical University approved this study, and all subjects signed an informed consent for their participation in the study.

Inclusion criteria: (1) Patients whose computed tomography (CT) angiography or coronary angiography results showed at least one of the three branches of the left anterior descending coronary artery, the left circumflex branch and the right coronary artery had coronary artery stenosis of more than 50%. (2) Patients who had not undergone surgical treatments, such as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), and had no indication for surgical interventions shortly. (3) Patients who could follow the instructions of doctors, take medication regularly and timely, do follow-up tests for indicators such as blood lipids, liver function, renal function, and blood routine examination, and record all adverse reactions accurately. (4) Patients whose initial testing of blood lipids showed compliance with at least one of the following results: low-density lipoprotein cholesterol (LDL-C) ≥ 130 mg/dL (3.37 mmol/L), cholesterol ≥ 201 mg/dL (5.18 mmol/L), triglycerides ≥ 200 mg/dL (2.27 mmol/L).

Exclusion criteria: (1) Patients who had taken other lipid-lowering drugs before the consultation. (2) Patients with various acute and chronic hepatitis and kidney diseases, liver dysfunction and renal insufficiency. (3) Patients with various tumorous lesions, biliary obstruction, acute and chronic pancreatitis, acute and chronic gastroenteritis, and other malabsorption disorders or over-exhaustive underlying diseases. (4) Women of child-bearing age who were pregnant or were preparing to become pregnant within one year of follow-up. (5) Patients with various peripheral vascular diseases and myopathy. (6) Patients with poor compliance or who were unable to be followed-up for indicator examination. (7) Patients who were diagnosed with acute myocardial infarction or other severely high-risk heart diseases.

Treatment

Patients in the control group received atorvastatin (Lipitor®, Pfizer, USA) in doses of 20 mg once a day, before bedtime in addition to conventional medication for 3 months. In addition to the above treatment, patients in the experimental group received CoQ₁₀ (Guangdong

CAXIN Biotechnology, China) in doses of 15 mg for 3 times *per day*, after meals for 3 months. During the study period, patients should not eat foods rich in CoQ₁₀, such as animal offal, chicken and fish.

Biochemistry parameters

The fasting venous blood samples were collected from each patient before the treatment and 3 months after the treatment. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and blood lipid indicators as total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were determined using an automatic analyser (Beckman, USA) using routine reagent kits and assays. In the same time, the markers of liver function, renal function, cardiac function, blood routine examination, and urine routine exam were determined for each patient before and 3 months after the treatment.

The level of plasma CoQ₁₀ was determined by HPLC (Hitachi, Japan) from plasma, after n-hexane extraction, as follows: 0.3 mL of the plasma sample was pipetted into the centrifuge tube, mixed with 1 mL of n-hexane (Liaoning Yufeng Chemical Co., Ltd., China), vortexed for 2 min, and centrifuged at 8000 r/min for 10 min. Then, the supernatant was pipetted and analysed.

The adverse reactions during the medication, such as myalgia, myolysis, nausea and epigastric discomfort, were recorded. The serious cardiovascular events, such as arrhythmias, acute myocardial infarction, heart failure, and even death, were also recorded.

The number of patients who were forced to undergo vascular reconstruction therapy, i.e., percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), due to their medical conditions during the three months of medication was recorded.

Doppler echocardiography

All patients underwent a Doppler echocardiography by Doppler ultrasonic diagnosis apparatus (Siemens, Germany) for the determination of left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD) before the treatment and 3 months after the treatment.

Measurement of hemodynamic indicators

A digital non-invasive hemodynamic detector (Shenzhen Maidean Medical Equipment Co., Ltd., China) was used to measure the cardiac function parameters of patients in the experimental group and the control group before and 3 months after the treatment. These parameters included thoracic fluid level (TFC), acceleration index (ACI), velocity index (VI) and heart rate (HR), systolic time ratio (STR), pre-ejection period (PEP), left ventricular ejection time (LVET), mean arterial pressure (MAP), cardiac output (CO), cardiac index (CI), stroke volume (SV), cardiac index (SI), left ventricle stroke work index (LVSWI), left ventricular work index (LVWI) were measured.

Indicators that requested treatment discontinuation

(1) patients who had visible intolerable adverse reactions; (2) creatine kinase (CK) > triple the upper limits of normal reference ranges (25 - 200 U/L for males and 25 - 170 U/L for females), (3) severe liver damage: alanine aminotransferase (ALT) > 120 U/L (triple the upper limit of the normal reference range - 40 U/L); aspartate aminotransferase (AST) > 105 U/L, (triple the upper limit of the normal reference range - 35 U/L); and bilirubin > 3 times the upper limit of the reference range (1.71 - 7 µmol/L).

Statistical methods. The obtained clinical data were analysed by IBM SPSS 19.0 statistics software package (IBM, USA). The obtained blood lipid indicators were evaluated for normality and homogeneity by normal and homogeneity test of variance. All measurement

data were expressed as mean number ± standard deviation. Intra-group data processing were performed using independent-sample t-test. The paired-samples t-test was used for intra-group comparison. The Chi-square test was used for the group comparison of count data. A value of $p < 0.05$ was considered statistically significant.

Results and Discussion*General clinical data*

There were no significant differences in general clinical data (age, gender, BMI, hypertension, history of smoking, family disease history, diabetes mellitus and carotid artery plaque) between the two groups of patients at the beginning of the study (Table I).

Table I

Statistical results of general clinical data

Indicators	The experimental group	The control group
Age (years)	56.74 ± 7.98	59.25 ± 8.76
Gender (male/female)	24/18	22/20
BMI	22.08 ± 0.57	22.15 ± 0.54
History of smoking (cases)	17	19
Hypertension (cases)	28	23
Diabetes mellitus (cases)	14	16
Family disease history (cases)	7	3
Carotid atherosclerotic plaque (cases)	14	15

CoQ₁₀ and transaminase levels before and 3 months after the treatment

There were no significant differences in CoQ₁₀ level and serum aminotransferase levels between the two groups before the treatment ($p > 0.05$). In the experimental group, after 3 months of treatment, the levels of CoQ₁₀ significantly increased compared with those before the treatment ($p < 0.05$). There was no significant increase in ALT and AST levels after the treatment compared to the levels before

the treatment in the experimental group ($p > 0.05$). In the control group, after 3 months of treatment, the level of CoQ₁₀ decreased significantly compared to the levels before the treatment ($p < 0.01$) and the levels of ALT and AST increased significantly ($p < 0.01$). After the treatment, CoQ₁₀ levels were significantly increased in the experimental group compared to the control group, while the levels of ALT and AST significantly decreased ($p < 0.05$) (Table II).

Table IICoQ₁₀, transaminase levels and blood lipid markers before and after the treatment in the experimental and control group

Parameters		Experimental group	Control group
CoQ ₁₀ (µg/mL)	Before the treatment	0.48 ± 0.11	0.49 ± 0.11
	After the treatment	0.65 ± 0.17* ^{&}	0.40 ± 0.12*
ALT (IU/L)	Before the treatment	24.06 ± 9.82	18.54 ± 7.35
	After the treatment	24.29 ± 9.17 ^{&}	42.64 ± 12.64*
AST (IU/L)	Before the treatment	20.67 ± 7.08	19.14 ± 7.48
	After the treatment	21.68 ± 6.48 ^{&}	38.76 ± 10.24*
LDL-C (mmol/L)	Before the treatment	3.89 ± 1.26	3.87 ± 1.11
	After the treatment	2.0 ± 0.47* ^{&}	2.45 ± 0.54*
HDL-C (mmol/L)	Before the treatment	1.46 ± 0.36	1.46 ± 0.38
	After the treatment	1.73 ± 0.34	1.61 ± 0.46
TC (mmol/L)	Before the treatment	5.52 ± 1.65	5.58 ± 1.73
	After the treatment	3.59 ± 0.49* ^{&}	4.34 ± 0.54*
TG (mmol/L)	Before the treatment	3.91 ± 1.01	3.96 ± 0.98
	After the treatment	2.51 ± 0.51* ^{&}	2.99 ± 0.34*

* $p < 0.05$ compared with the levels before the treatment; [&] $p < 0.05$ compared with the control group

Variations in blood lipids before and 3 months after the treatment

After 3 months of treatment, the TC, TG, and LDL-C levels were all lower than those before the treatment

($p < 0.05$), while the HDL-C level increased without reaching the statistical significance ($p > 0.05$). Compared with the control group, the TC, TG, and LDL-C levels in the experimental group decreased

significantly ($p < 0.05$) and the HDL-C level increased, without reaching the statistical significance (Table II). LDL-C less than 2.6 mmol/L (100 mg/dL) was taken as the standard value. If LDL-C was less than 2.6 mmol/L, it was considered meeting the standard. Blood lipid compliance rate = (number of people meeting the standard/total number of people $\times$ 100%).

A total of 38 patients in the experimental group met the standard (90.47%), and a total of 27 patients in

the control group met the standard (64.28%). The comparison between the two groups showed significant differences ($p < 0.05$).

Cardiac function parameters before and after the treatment in the experimental and control group

After the treatment, the cardiac function parameters in the experimental group significantly improved compared to the control group ($p < 0.05$) (Table III).

Table III

Cardiac function parameters in the two groups

Parameters	Experimental group		Control group	
	Before the treatment	After the treatment	Before the treatment	After the treatment
LVEDD (mm)	72.23 $\pm$ 2.13	63.23 $\pm$ 1.54* $\&$	72.18 $\pm$ 2.04	68.26 $\pm$ 1.97*
LVESD (mm)	57.87 $\pm$ 1.85	51.04 $\pm$ 1.27* $\&$	58.28 $\pm$ 1.86	54.83 $\pm$ 1.84*
LVEF (%)	38.77 $\pm$ 1.64	45.03 $\pm$ 1.36* $\&$	38.54 $\pm$ 1.57	41.18 $\pm$ 1.84*

Left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular ejection fraction (LVEF).

* $p < 0.05$ compared with the results before the treatment; $\&p < 0.05$ compared with the control group

Hemodynamic parameters before and after the treatment in the experimental and control group

In both the experimental group and the control group, the hemodynamic parameters significantly increased

compared to the results before the treatment ($p < 0.05$).

After the treatment, the hemodynamic parameters significantly increased in the experimental group compared to the control group ($p < 0.05$) (Table IV).

Table IV

Hemodynamic parameters in the two groups

Parameters	Experimental group		Control group	
	Before the treatment	After the treatment	Before the treatment	After the treatment
CO (L/min)	4.75 $\pm$ 0.54	5.66 $\pm$ 0.63* $\&$	4.87 $\pm$ 0.57	5.24 $\pm$ 0.62*
CI [L/(min $\cdot$ m ²)]	2.21 $\pm$ 0.46	3.14 $\pm$ 0.54* $\&$	2.09 $\pm$ 0.51	2.79 $\pm$ 0.42*
SV (mL)	66.22 $\pm$ 8.54	74.65 $\pm$ 8.63* $\&$	64.45 $\pm$ 9.08	70.12 $\pm$ 7.14*
SI (mL/m ²)	38.61 $\pm$ 7.43	44.51 $\pm$ 7.26* $\&$	35.60 $\pm$ 7.35	40.32 $\pm$ 6.25*
LVS WI [g/(min $\cdot$ m ²)]	40.33 $\pm$ 9.35	47.77 $\pm$ 9.61* $\&$	40.08 $\pm$ 7.42	43.31 $\pm$ 4.26*
LCWI [kg/(min $\cdot$ m ²)]	2.65 $\pm$ 0.61	3.41 $\pm$ 0.65* $\&$	2.73 $\pm$ 0.54	3.03 $\pm$ 0.37*
VI ($\times 10^{-3}$ s)	41.92 $\pm$ 8.22	47.59 $\pm$ 5.48* $\&$	40.13 $\pm$ 6.15	44.57 $\pm$ 5.65*

Cardiac output (CO), Left Ventricular Ejection Time (LVET), Cardiac Index(CI), Stroke Volume(SV), Cardiac Index(SI), Left Ventricle

Stroke Work Index(LVSWI), Left Ventricular Work Index(LVWI) and Velocity Index(VI). Compared with the results before the treatment,

* $p < 0.05$; compared with the control group, $\&p < 0.05$

Side effects

There were no reported myalgia and rhabdomyolysis in the two groups during the 3 months of treatment. No adverse events, such as serious arrhythmias and fatal/non-fatal myocardial infarction, occurred in

both groups during the treatment. Only minor side effects as the increase of ALT levels above the normal range, gastrointestinal reactions and muscular weakness were observed in both groups without significant difference between the two groups (Table V).

Table V

Side effects incidents during the treatment in the two groups

Parameters	Experimental group	Control group
ALT > The normal value	1	2
ALT > Triple the normal value	0	0
CK > The upper limit of normal value	0	0
Gastrointestinal reactions	3	4
Myalgia	0	0
Muscular weakness	0	3
Rhabdomyolysis	0	0

Studies have shown that a person with increased serum TC and/or LDL-C levels, or those with reduced HDL-C levels present increasing morbidity and mortality of cardiovascular cause [10, 11]. Numerous experiments and clinical studies have proved that the LDL-C can promote the occurrence and development

of coronary atherosclerosis, while HDL-C can inhibit the occurrence and development of coronary atherosclerosis [12, 13]. Therefore, clinically, decreasing serum TC, LDL-C and TG levels while increasing the HDL-C levels is the main lipid regulation pathway

that helps in preventing and treating coronary atherosclerotic heart disease.

Atorvastatin belongs to the statin family [14]. It prevents the synthesis of cholesterol in the liver by inhibiting the activity of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase [15]. Atorvastatin reduces free cholesterol in the cell. Through negative feedback, the number of LDL-C receptors in the cell is increased and their activity is enhanced, which has promoted the elimination of LDL and very-low-density lipoprotein (VLDL) from the blood, thereby reducing the endogenous blood lipid content in the blood [16, 17]. The major feature of atorvastatin in lipid-lowering is to reduce TC and LDL-C levels and a lower effect on decreasing TG level [18, 19]. Atorvastatin can also increase the level of HDL-C [20]. Therefore, the onset and development of atherosclerosis can be stopped [21]. Usually, conventional doses of statins can reduce the LDL-C level by 20 - 35%. However, as the dose is doubled, the lipid-lowering effect does not increase linearly, while the adverse effects increase [22]. Therefore, the clinical use of statins alone for lipid regulation has certain limitations, which hinders the regulation of blood lipids in patients with CHD in clinical practices.

In this study, by comparing the treatment only with and the combination of statins and CoQ₁₀, it was found that the exogenous supplementation of CoQ₁₀ could reverse the decrease of CoQ₁₀ levels in the body caused by atorvastatin. In the same time, it is observed a limitation of the increase of transaminases activity caused by statins. ALT and AST are a group of enzymes that reflect liver cell damages. They are mainly present in the cytoplasm of hepatocytes. AST is also distributed in the mitochondria. Once CoQ₁₀ is lacking, different oxidative respiratory chain functions in the mitochondria of the cell become impaired, and the oxygen-free radicals increased, which produce liver damage and increase the ALT and AST levels. CoQ₁₀ supplementation can be used to maintain the integrity of cell structure and function, promote the repair of liver cells, and thus have a certain protective effect on the liver damage [23, 24]. On the other hand, CoQ₁₀ can also reduce the increase of intracellular calcium concentration caused by statin lipid-lowering drugs, prevent Ca²⁺ influx, and reduce liver cell damage caused by intracellular Ca²⁺ overload [25]. The results of this study also showed that the combination of CoQ₁₀ and atorvastatin had better results in reducing TC, TG, and LDL-C levels and increasing HDL-C levels. CoQ₁₀ prevents lipids and proteins from peroxidation and scavenges free radicals. It is used to reduce oxidative damage to different tissues and as an inhibitor of LDL cholesterol oxidation [26], which may be a mechanism for CoQ₁₀ to promote lipid metabolism.

The results of this experiment showed that after the treatment, the CO, CI, SV, SI, LVSWI, LCWI and

VI values of the experimental group and the control group were significantly higher than those before the treatment, with a significant increase in the experimental group compared with the control group. Besides, the left ventricular diastolic function of the experimental group was significantly improved after the treatment compared to the control group. Atorvastatin had no significant side effects on the central functions of CHD patients, and its possible mechanisms include (1) antioxidant effects and inhibition of inflammatory response [27]; (2) improvement of vascular endothelial function [28]; (3) neuroendocrine regulation and inhibition of ventricular remodelling [29]. Atorvastatin associated with CoQ₁₀ can promote the improvements of cardiac functions and hemodynamic in earlier stages. The mechanism may be related to the improvement of myocardial energy metabolism by CoQ₁₀ [30]. It has been shown that the cardiac functions of CHD patients who were treated with atorvastatin and CoQ₁₀ could be improved effectively.

Conclusions

There were no significant differences in adverse reactions between the control group and the experimental group. During the course of treatment, no serious adverse reactions occurred. Both groups were safe in the treatment of CHD. Therefore, the use of a combination of atorvastatin and CoQ₁₀ could be promoted in clinical practice.

Acknowledgement

This work was supported by Scientific Research Project of Heilongjiang Health and Family Planning Commission (Project No.: 2014-191).

Conflict of interest

The authors declare no conflict of interest.

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