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Lipids

A Novel Medical Treatment for Lipid Control in Patients with Unstable Angina Pectoris and Statin-Induced Liver Dysfunction

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Background: This study aims to evaluate the safety and efficacy of Xuezhikang in the treatment of unstable angina pectoris (UAP) in patients with elevated liver enzymes caused by statins.

Methods: Ninety UAP patients with elevated liver enzymes (higher than 3-fold the upper limits of normal caused by statins) were randomly divided into 3 groups: withdrawal of simvastatin (group A), continued taking of simvastatin (group B) and switching to Xuezhikang capsules (group C).

Results: Blood lipids and high-sensitivity C-reactive protein (hs-CRP) were measured before and after treatment, and liver enzymes were measured every two weeks. As the liver enzymes of the patients in group A returned to normal, they could again undertake administration of simvastatin. If the liver enzyme levels remained abnormal at four weeks, polyene phosphatidylcholine would be added. The endpoint events of each group were followed-up. After treatment for 4 weeks, the liver enzymes decreased in all of the three groups and there was a significant difference ($p < 0.05$). However, at 8 weeks the liver enzymes showed no significant difference among the three groups ($p > 0.05$). The blood lipids and hs-CRP were both reduced in group B and C. The decreased triglyceride and hs-CRP levels and increased high-density lipoprotein cholesterol level in group C were more remarkable than those in group B ($p < 0.05$). The incidence rate of endpoint events in group A was the highest ($p < 0.05$) among the three groups.

Conclusions: Xuezhikang is safe and effective in the treatment for UAP patients with elevated liver enzymes caused by statins.

Key Words: Liver enzymes • Simvastatin • Unstable angina pectoris • Xuezhikang capsules

INTRODUCTION

Statins are a cornerstone in the treatment of cardiovascular disease,[1,2] but the overall safety of their use remains a hotly debated issue. In the event of an adverse drug reaction, the problematic statin is frequently withdrawn and replaced with another drug. In 2012, the United States (U.S.) Food and Drug Administration (FDA) withdrew the proposal that patients taking statins should monitor their liver enzymes periodically. However, a panel of liver experts at the U.S. National Institute of Lipids recommended that if liver enzymes are observed at levels higher than 3 times the upper limits of normal (ULN), administration of statins should be suspended to allow the liver enzymes to return to the normal level. Then the patients can re-take statins or replace the statin medication with other lipid-lowering drugs. Unfortunately, interruption of statin therapy would result in an increase in cardiovascular adverse events.[3] In fact, elevated liver enzymes do not necessar-

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ily mean liver failure.[4] In 2009, Chinese experts reached a consensus that Xuezhikang could be tried as a treatment option for those patients that are intolerant to statins, those patients with dyslipidemia, as well as those patients with elevated liver enzymes and muscle enzymes caused by statins. However, the question remained whether statins should be stopped or just replaced with Xuezhikang for those unstable angina pectoris (UAP) patients with liver enzymes $\geq 3 \times$ ULN. Therefore, we conducted a clinical study to observe the safety and efficacy of Xuezhikang.

MATERIALS AND METHODS

General data

There were 90 UAP patients with elevated liver enzymes enrolled in this study, who had been hospitalized in the department of Cardiology of our hospital from June 2008 to June 2013. All patients met to the diagnostic criteria of "the diagnosis and treatment recommendations for unstable angina" published by the Chinese Society of Cardiology. The thrombolysis in myocardial infarction (TIMI) score of patients was 0-4 points. The liver enzyme level of each patient was 3- to 9-fold of the ULN caused by taking 20 mg simvastatin capsules (Shandong Lukang Pharmaceutical Co., Ltd. China), once every night, but their direct bilirubin and indirect bilirubin levels were normal. Patients with hepatitis, alcoholism, cholangitis, pancreatitis as well as other drugs-derived and non-liver-derived elevated transaminase were excluded from this study. Our subjects included 50 males and 40 females with an age range from 52 to 80 years. The subjects were randomly divided into 3 groups (n = 30 for each group) as they were admitted into our hospital. This study was conducted in accordance with the declaration of Helsinki and with approval from the Ethics Committee of the People's Hospital of Xingtai City. Written informed consent was obtained from all participants.

Study design

Patients in our study were asked to eat a low-fat light diet, quit smoking and alcohol consumption, and cease the taking of other drugs that might influence patient blood lipids. Meanwhile, all of the patients received a conventional anti-anginal therapy, including but not limited to nitrates, β-acceptor blockers, calcium antagonists, enteric-coated aspirin and low molecular weight calciparine. Patients in group A stopped taking simvastatin. When their liver enzymes had returned to the normal level, they restarted simvastatin use with a nightly dosage of 20 mg. Patients in group B continued to take 20 mg simvastatin every night. If their liver enzymes were not restored to normal level after four weeks' treatment, polyene phosphatidylcholine (Sanofi-Aventis Pharma Co., Ltd., Beijing, China) was added for a twice daily dosage of 228 mg. Patients in group C stopped taking simvastatin, but started taking 0.6 g Xuezhikang capsules (Peking University WBL Biotech Co., Ltd., Beijing, China) twice daily. The total treatment course was 8 weeks. If patients developed jaundice, liver enlargement, fatigue, symptoms of lethargy or other signs of liver damage or unexplained muscle pain, or muscle weakness accompanied by creatine kinase (CK) elevation, treatment should be terminated.

Outcome measures

Blood lipids [consisting of total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C)] and high-sensitivity C-reactive protein (hs-CRP) were measured before and after treatment and liver enzymes were assessed every two weeks. The incidence rate of the endpoint events of each group, including death, fatal myocardial infarction (MI), nonfatal MI, sudden death and other coronary heart disease (CHD)-caused death, were subsequently followed-up.

Statistical analysis

Statistical analysis was performed using the SPSS software program v 13.0 (Chicago, IL, USA). Continuous variables were shown as mean ± standard deviation (SD) and compared using paired *t*-test (between, before and after the treatment) or one-way ANOVA (among three groups) or Tukey's test (between two groups). A Chi-square or a Fisher's test was used to estimate the difference between incidence rates of endpoints according to relevant application conditions. p-values less than 0.05 were considered statistically significant.

RESULTS

Baseline characteristics of patients

The baseline characteristics of patients, including gender, age, history of smoking, history of drinking, history of hypertension, blood glucose, blood lipids, alanine aminotransferase (ALT) and hs-CRP in three groups were shown in Table 1. There was no significant variation among the above indexes between the three groups ($p > 0.05$).

Comparisons of TC, HDL-C, LDL-C, TG and hs-CRP

After 8 weeks' treatment, the serum TC, LDL-C, TG and hs-CRP levels were reduced remarkably in group B and group C ($p < 0.05$) but not in group A ($p > 0.05$). As compared with group B, the serum TG and hs-CRP in group C were reduced more significantly ($p < 0.05$). The HDL-C level was enhanced prominently in group C ($p < 0.05$) but not in group B or A ($p > 0.05$) (Table 2).

Comparisons of ALT

The serum ALT level was notably reduced in all of the three groups either at the 4-week or 8-week interval after treatment ($p < 0.05$). However, it was reduced more rapidly in group A and group C at the first 4 weeks, which showed a statistical difference from that in group B ($p < 0.05$). In group B, approximately 20% of patients had to take polyene phosphatidylcholine at that time. Nevertheless, ALT levels showed no marked difference between the three groups at 8 weeks post-treatment ($p > 0.05$) (Table 3).

Table 1. Baseline characteristics of patients*

Index	Group A	Group B	Group C
n (male/female)	30 (16/14)	30 (17/13)	30 (17/13)
Age (year)	66.12 ± 9.11	65.36 ± 8.75	67.04 ± 8.61
History of smoking (%)	12 (40.0)	13 (43.3)	12 (40.0)
History of drinking (%)	16 (53.3)	16 (53.3)	17 (56.7)
History of hypertension (%)	22 (73.3)	21 (70.0)	20 (66.7)
FBG (mmol/L)	5.84 ± 1.20	5.78 ± 1.17	5.86 ± 1.28
TG (mg/dl)	188 ± 32	191 ± 36	189 ± 38
TC (mg/dl)	202 ± 27	201 ± 26	200 ± 21
LDL-C (mg/dl)	154 ± 27	151 ± 24	152 ± 23
HDL-C (mg/dl)	43 ± 13	42 ± 9	41 ± 12
ALT (U/L)	248 ± 114	250 ± 118	254 ± 116
hs-CRP (mg/L)	16.57 ± 9.23	16.79 ± 9.94	16.52 ± 9.41

* There was no significant difference of indexes among the three groups ($p > 0.05$).
ALT, alanine aminotransferase; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

Table 2. Comparisons of TC, HDL-C, LDL-C, TG and hs-CRP between before and after treatment in three groups

Group		TC (mg/dl)	TG (mg/dl)	LDL-C (mg/dl)	HDL-C (mg/dl)	hs-CRP (mg/L)
Group A	Before	202 ± 27	188 ± 32	154 ± 27	43 ± 13	16.57 ± 9.23
	After	199 ± 24	181 ± 29	145 ± 25	45 ± 10	15.68 ± 9.01
Group B	Before	201 ± 26	191 ± 36	151 ± 24	42 ± 9	16.79 ± 9.94
	After	156 ± 23*	168 ± 27*	118 ± 22*	44 ± 11	13.43 ± 8.59*
Group C	Before	200 ± 21	189 ± 38	152 ± 23	41 ± 12	16.52 ± 9.41
	After	170 ± 20*	146 ± 25*#	119 ± 21*	49 ± 10*#	10.24 ± 7.96*#

Data were showed as mean ± SD. * $p < 0.05$, compared with before treatment; # $p < 0.05$, compared among three groups after treatment.
HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

Endpoint events

The incidence of endpoint events including nonfatal MI, fatal MI and death in group A, B and C was 13.3% (4/30), 3.3% (1/30) and 3.3% (1/30), respectively. This rate was remarkably higher in group A than in the other two groups ($p < 0.05$) (Table 4).

DISCUSSION

Statins play a noteworthy role in the treatment of cardiovascular disease since they can stabilize vulnerable plaques, reduce the risk of thromboembolism, and even reverse plaque buildup.[5] In 2011, a European dyslipidemia management guide was published jointly by the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS), in which the baseline LDL-C level was no longer a standard condition for statins therapy. It is recommended that patients with acute coronary syndrome should be treated with statins immediately when they are hospitalized because intensive statin treatment can achieve enhanced benefits for cardiovascular disease.[6-9] However, its adverse reactions remain controversial. The incidence rate of elevated liver enzymes increased as statin dosages increased.[10]

Table 3. Comparisons of ALT (U/L) between before and after the treatment as well as between groups

Group	Before	4 weeks	8 weeks
Group A	248 ± 114	26 ± 8*	24 ± 6
Group B	250 ± 118	58 ± 23*#	28 ± 9*
Group C	254 ± 116	28 ± 10*	26 ± 7

Data were showed as mean ± SD. * $p < 0.05$, compared with before treatment; # $p < 0.05$, compared among the three groups after 4 weeks' treatment.
ALT, alanine aminotransferase.

Table 4. Cardiovascular outcome in three groups

Group	Nonfatal MI (n)	Fatal MI (n)	Death (n)	Incidence of endpoint events (%)
Group A	2	1	1	13.3%*
Group B	1	0	0	3.3%
Group C	0	1	0	3.3%

* $p < 0.05$, compared among the three groups after 8 weeks' treatment.
MI, myocardial infarction.

Asian patients are more frequently intolerant to statins and have high incidence rates of elevated liver enzymes and abnormal muscle enzyme. The China Coronary Secondary Prevention Study (CCSPS)[11] reported that a conventional dose of Xuezhikang can reduce the clinically adverse events in Chinese patients with CHD and has an excellent record for safety. CCSPS and MEGA studies have suggested that Oriental people can be treated with smaller doses of statins than patients in European countries because Oriental people primarily are afflicted with mild to moderate dyslipidemia.[12,13] The conventional dose of statins can effectively reduce the number of adverse events in Oriental people.

In this study, the application of Xuezhikang (group C) or continued application of simvastatin (group B) in the UAP patients with elevated liver enzymes can effectively reduce TC and LDL-C levels, and they cause a similar incidence rate of endpoint events. However, after withdrawal of simvastatin (group A), patient blood lipids did not manifestly decrease, and the incidence of endpoint events were significantly higher than in the other two groups. The majority of patients had elevated liver enzymes after taking statins for just 2 weeks, after which the treatment was immediately stopped (which is too early). Considering the apprehension of partial patients, the use of statins is not timely recovered. So the actual statin use period is very short, only about 2 weeks. The cardiovascular events occurred primarily during the statins withdrawal period. At the same time, some patients are much older, and non-cardiovascular death may interfere with the statistics of endpoint events. On the other hand, the TIMI system has certain limitations for risk stratification and prognosis evaluation of UAP. Those patients with a lower-intermediate risk in TIMI score may be actually be at a high risk for cardiovascular events. So the incidence of endpoint events would be high.

Xuezhikang has similar impact on the liver enzyme recovery when statin use is withdrawn, suggesting that Xuezhikang has superior efficacy and safety. The liver enzymes of those patients treated continually with the original dose of simvastatin (group B) decreased more slowly than in the other two groups; approximately 20% of patients in this group had to take polyene phosphatidylcholine at this time. The chemical structure of polyene phosphatidylcholine is consistent with endogenous phospholipid. It mainly enters the liver cells, and com-

bines with liver cell membrane and organelle membrane as a complete molecule. So the impaired liver function and enzyme activity thereafter restore to normal. However, use of polyene phosphatidylcholine will saddle patients with a greater economic burden. Fortunately, no hepatic failure occured in the three groups, indicating a rare occurrence of liver damage caused by statins.[14] Even though the observed liver enzymes are higher than 3-fold of level of ULN or even reach to 5- to 9-fold of ULN, statin therapy cannot be prematurely terminated. The statin-induced elevation of liver enzymes is not due to liver cell necrosis, but the pharmacokinetic change of cholesterol synthesis inhibitor in liver, which has a transient influence. If the patient's bilirubin level increases or obstructive jaundice occurs, further statins use may lead to hepatotoxicity and should be avoided.[15]

Xuezhikang is refined from special red yeast rice, which was first discovered in China and widely used since the Tang Dynasty for more than a thousand years. The utilization of red yeast rice has also been fully documented in "Compendium of Materia Medica", written by Shizhen Li, and "Important Annotation of Herbal" written by Ang Wang suggesting that it has multiple effects on blood pressure, lipid-lowering, anti-oxidation, and further has anti-cancer characteristics. Xuezhikang is a pure natural Chinese medicine, which is a historical application of red yeast rice and called a "Chinese statin" by foreigners. It is reported that Xuezhikang contains 13 kinds of natural composite statins homologues and a variety of unsaturated fatty acids, sterols, alkaloids, essential amino acids, flavonoids and trace elements such as selenium, zinc and manganese, which can regulate blood lipids and protect vascular endothelium through a variety of different mechanisms.[16] In this study, we found that Xuezhikang is superior to simvastatin in reducing the TG[17] and hs-CRP level and enhancing the HDL-C level, which is consistent with the other documents. High TG and low HDL-C reflect the residual risk of intensive statin therapy to some extent,[18-21] and inflammation may be the main driver of the cardiovascular residual risk. hs-CRP is a sensitive and non-specific marker for systemic inflammation, tissue damage and infection,[22] which plays an important role in the pathogenesis of UAP. Information from Europe ECTA study showed the relative risk of nonfatal MI and sudden cardiac death increase by 45% with every increased standard deviation of hs-CRP concentration either in patients with stable angina pectoris or the patients with UAP. Patients can be classified into different risks of cardiovascular disease according to the hs-CRP levels and an early intervention against the inflammatory cytokines such as hs-CRP can achieve more clinical benefits.[23] Xuezhikang has some advantages in reducing the TG and hs-CRP level and elevating HDL-C level. Therefore, it can be used as an alternative for UAP patients with elevated liver enzymes caused by statins.

Only a small number of patients suffered from elevated liver enzymes more than 3-fold of the ULN caused by statins; thus this study had to last for five years. Additionally, the sample size and the observation time in this study was not sufficiently large. For some older patients, the calculation for non-cardiovascular death can interfere with the statistics of endpoint events. In addition to mild to moderate dyslipidemia and low-intermediate medium risk of angina in this population, patients with percutaneous coronary intervention or coronary artery bypass grafting were not included, so there may be some bias in our findings. Therefore, more trials are necessary in the future.

This study has confirmed the necessity of using statins in UAP patients. Premature early withdrawal of the drug will increase the incidence of cardiovascular events. The statins induced liver enzymes elevation is mostly transients, and can be restored to normal. It rarely causes liver function damage or liver failure. For UAP patients with liver enzymes $\geq 3 \times$ ULN and even with 5-9 $\times$ ULN, statin use should not be terminated. As a lipid-lowering Chinese traditional medicine, Xuezhikang can be applied in some UAP patients. It has obvious efficacy, with little effect on the liver function.

CONCLUSIONS

Xuezhikang is safe and effective in the treatment for UAP patients with elevated liver enzymes caused by statins.

CONFLICT OF INTEREST

The authors have declared that no competing interests exist.

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