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Original Article

Intervention study of combination therapy using tongxinluo and atorvastatin with brain ultrasounds on carotid vulnerable plaque

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Abstract: Objective: The current study aimed to investigate the therapeutic effects of the combined application of tongxinluo, atorvastatin, and brain ultrasounds on carotid vulnerable plaque. Methods: A total of 324 participates were enrolled in this study. Patients (80 cases) only taking ordinary oral lipid-lowering drug atorvastatin were assigned to the control group. Three experimental groups were established, group A (tongxinluo, atorvastatin and brain ultrasound), group B (tongxinluo and brain ultrasound), and group C (atorvastatin and brain ultrasound), with 82, 82, and 80 cases in each corresponding group. Oral administration of tongxinluo was given 3 times a day, with 4 capsules each time. Atorvastatin was given 1 time a day, with 20 mg each time. Routine brain ultrasound treatment (SUT-800 type) was given once a day. Results: Intervention effects of the four groups on fatty plaques showed significant differences. Combination of three treatment methods had significantly higher intervention effects on fatty plaques than the other three groups ($P < 0.05$). There were no significant differences between group B and group C ($P > 0.05$). Conclusion: Combination therapy of tongxinluo, atorvastatin, and brain ultrasounds could remarkably melt or reduce fatty plaques in carotid arteries, showing great clinical potential.

Keywords: Tongxinluo, atorvastatin, brain ultrasound therapy, carotid vulnerable plaque

Introduction

Atherosclerosis (AS) and plaque formation are major causes of ischemic cerebrovascular disease (ICVD). When carotid AS occurs, fat will deposit in the intima to form a fat line, leading to intima-media thickness (IMT). This endometrial alteration is an early manifestation of AS that will lead to atherosclerotic plaque [1-3]. With effective prevention and treatment of carotid atherosclerotic plaques, the plaque will change from unstable to stable, or even reverse. This may reduce occurrence and development of carotid atherosclerosis (CAS) [4].

The ICVD of CAS is closely related to the stability of atherosclerotic plaque. The vulnerability of plaque is the main risk factor of cerebral infarction. In early stages, focal deposition of intimal lipids and hyperplasia of smooth muscle cells and fibrosis could lead to the formation of lipid streaks. When the lesion progresses to a certain extent, plaque will form. Based on this, plaque hemorrhages, rupture loss, mural thrombosis, and secondary vascular stenosis could result in distal hypoperfusion and other changes, causing corresponding changes in blood rheology. This will ultimately lead to ischemic cerebrovascular disease [5, 6]. Low-density, easy bleeding, and rapid changes in the volume of short-term increased plaque causing high risks of cerebral infarction have been widely recognized by scholars [7, 8].

At present, most studies use atorvastatin to treat atherosclerotic plaques. Atorvastatin can stabilize plaque, however, the function of ablation plaque has been rarely reported. Moreover, atorvastatin can cause liver damage, muscle and joint pain, gastrointestinal reactions, and other adverse reactions. According to clinical practice, it was found that application of tongxinluo (a Traditional Chinese preparation) for treatment of atherosclerotic plaque could reduce doses of atorvastatin and incidence of adverse events. Additionally, fat plaque can be

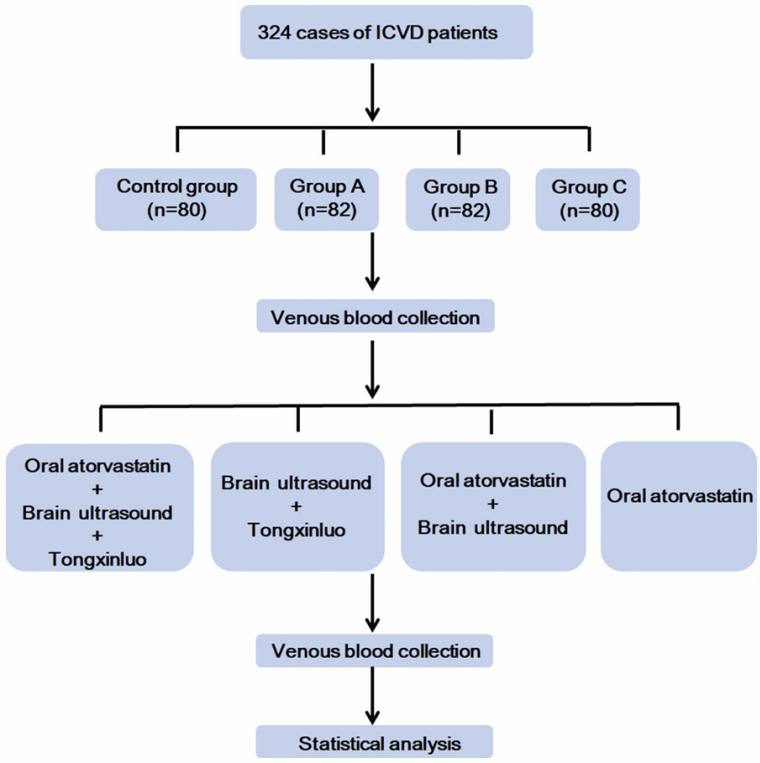

Figure 1. Schematic diagram of the study design.

ablated by physical, chemical, thermal, and shock effects of brain ultrasound treatments. The present study used tongxinluo and atorvastatin, combined with brain ultrasound treatment, aiming to discover a better treatment for atherosclerotic plaque.

Materials and methods

Subjects

Participants were recruited between June 2012 and June 2016, from Cangzhou Central Hospital in China. A total of 324 patients with ICVD entered the trial, including 193 males and 141 females, ranging in age from 53 to 82 years-old. The participants were randomly divided into four experimental groups, including group A (tongxinluo, atorvastatin, and brain ultrasound), group B (tongxinluo and brain ultrasound), group C (atorvastatin and brain ultrasound), and the control group (only taking atorvastatin), with 82, 82, 80, and 80 cases in each corresponding group. ICVD was diagnosed according to the criteria of "key points of diagnosis of various types of cerebrovascular diseases" [9]. Carotid artery plaque was confirmed by cervical vascular color ultrasonic inspection (CVUS). Two investigators, independently, collected participant clinical and demographic data via follow-ups or searches for medical records. Before participating in the study, all participants or their relatives provided written informed consent. The study was approved by the local Ethics Committee.

Treatment scheme

The schematic diagram of this study is shown in **Figure 1**. Briefly, the participates were divided into 4 groups and administration was undertaken as follows: 1) Oral atorvastatin [10] (Dalian Pfizer Pharmaceuticals Limited, Dalian, China) at a dose of 10 mg, once daily for 6 months; 2) Four tongxinluo capsules (Yiling Pharmaceutical Co., Ltd., Shijiazhuang, China), three times daily for 6 months; 3) Cerebral ultrasonic therapy at an output frequency of 800 KHz and sound intensity of 0.75-1.25 w/cm^2, once daily for 30 minutes each time [11]. There were 10 days to a cycle. The second cycle was started one week after the end of the first cycle. Fluid replacement was given for those that could not eat and dehydrants were given for those with cerebral edema. Examinations were performed 6 months after initiation of treatment.

CVUS examinations

All participants received CVUS before treatment (baseline) and 6 months after treatment using a PHILIPS IU22 Color Doppler Ultrasound Imaging System (transducer frequency 10 MHz). The participants took a supine position and received transverse and longitudinal ultrasound scans of bilateral common carotid arteries, internal carotid arteries, external carotid arteries, and bifurcation. Carotid artery intima-media thickness (IMT) was measured at 1-2 cm from the bifurcation. Atherosclerotic plaque was defined as local intimal protuberance and

Table 1. Baseline characteristics of patients in each group

	Group A (n = 82)	Group B (n = 82)	Group C (n = 80)	Control group (n = 80)	F/χ^2	P
Age	67.5 ± 9.6	65.7 ± 8.7	65.7 ± 8.7	65.7 ± 8.7	0.53[1]	0.664
Sex (%)						
Male	51 (62.2)	44 (53.7)	49 (61.3)	49 (61.3)	1.02[2]	0.796
Female	31 (37.8)	36 (46.3)	33 (38.7)	31 (38.7)		
Diagnosis (%)						
TIA	30 (36.6)	29 (35.4)	31 (38.8)	21 (26.3)	3.94[2]	0.685
Cerebral infarction	49 (59.8)	48 (58.5)	46 (57.5)	54 (67.5)		
Cerebrovascular dizziness	3 (3.6)	3 (6.1)	5 (6.7)	5 (6.2)		
Carotid artery disease (%)						
Bilateral	56 (68.3)	58 (70.7)	50 (62.5)	57 (71.3)	3.00[2]	0.392
Unilateral	26 (31.7)	22 (29.3)	32 (37.5)	23 (28.7)		
Complications (%)						
Hyperlipidemia	68 (48.9)	43 (34.9)	65 (44.8)	63 (45.3)	8.69[2]	0.192
Hypertension	35 (25.2)	49 (39.8)	47 (32.4)	39 (28.1)		
Diabetes	36 (25.9)	31 (25.2)	33 (22.8)	37 (26.6)		
TG[3] (mmol/L)	2.55 ± 0.38	2.48 ± 0.35	2.47 ± 0.35	2.55 ± 0.39	1.13[1]	0.337
TC[4] (mmol/L)	6.14 ± 0.51	6.17 ± 0.63	6.19 ± 0.48	6.16 ± 0.52	0.12[1]	0.948
HDL-C[5] (mmol/L)	1.37 ± 0.31	1.36 ± 0.54	1.37 ± 0.44	1.38 ± 0.32	0.03[1]	0.993
LDL-C[6] (mmol/L)	2.38 ± 0.52	2.38 ± 0.53	2.37 ± 0.58	2.39 ± 0.53	0.02[1]	0.997
Plaque (%)						
Vulnerable	86 (67.2)	89 (65.9)	83 (66.9)	81 (68.1)	0.134[2]	0.987
Stable	42 (32.8)	46 (34.1)	41 (33.1)	38 (31.9)		

Note: group A (tongxinluo, atorvastatin, and brain ultrasound), group B (tongxinluo and brain ultrasound), group C (atorvastatin and brain ultrasound), and control group (only taking atorvastatin); [1]ANOVA; [2]chi-square test; [3]TG: triglyceride; [4]TC Total cholesterol; [5]HDL-C: high-density lipoprotein cholesterol; [6]LDL-C: low-density lipoprotein cholesterol.

thickening with carotid intima-media thickness (IMT) ≥ 1.1 mm. Echoic patterns of the plaque, degrees of stenosis, color Doppler flow, and spectral parameters were observed. Depending on the morphology and echoic patterns of the plaque, they were divided into the following types: lipid type, lipid fiber type, fibrous type, and calcified type [4]. Hypoechoic plaque of lipid and fibrous types were vulnerable plaques, while hyperechoic plaques of the fibrous and calcified type were more stable [2].

Blood lipid testing

From each case, 6 mL of fasting venous blood sample was drawn before treatment and 12 months after treatment. Total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C) levels were detected using enzyme colorimetry. High-density lipoprotein cholesterol (HDL-C) was detected using the clearance method. Detection was carried out using an automatic biochemical analyzer (Hitachi 7060). Reagents were provided by Beijing Leadman Biochemistry Co., Ltd.

Statistical analysis

All statistical analyses were carried out using SPSS statistical software, version 16.0. All *p*-values were two-sided and statistical significance is set at $p < 0.05$. Measurements are expressed as mean ± standard deviation (± s). Two-factor analysis of variance and one-way ANOVA were used for repeated measurement data. For categorical data, Chi-square testing was performed.

Results

Clinical findings

To confirm the comparability between groups, baseline data for all participants were collected and compared. **Table 1** shows detailed baseline data for each group. Supplemental Table 1 illustrates the original data of the cohort. There were no significant differences in age, sex, carotid disease location, and complications between the four groups ($P > 0.05$). Moreover, blood lipid levels and the number and nature of

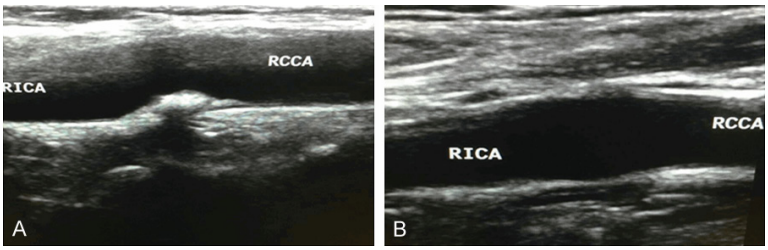

Figure 2. Cervical vascular color ultrasonic inspection (CVUS) performance of the patients before (A) and after treatment (B). Results showed fewer vulnerable plaques and more stable plaques after treatment.

carotid plaques in each group were compared. No statistically significant differences were noted between the groups before treatment ($P > 0.05$). Results suggest that baseline characteristics of patients in each group were comparable.

CVUS findings

To identify the number and nature of carotid plaque changes before and after treatment, CVUS was conducted for all participants. Carotid IMT was decreased or the plaques disappeared after treatment in the research group, compared with the other groups. As illustrated in **Figure 2**, there were fewer vulnerable plaques and more stable plaques after treatment. The major diameter of the plaques and the plaque score in group A decreased significantly, compared with the other 3 groups (**Table 2**, $P < 0.01$). There were no significant differences in detection ratios of vulnerable plaques and stable plaques between the four groups before treatment (**Table 3**). However, significant differences were noted between the four groups after treatment. Compared with the control group, the χo of the research group, tongxinluo group, and atorvastatin group was 36.262, 30.138, and 29.605, respectively. No significant differences between the three groups were identified (**Table 3**). The atorvastatin group and tongxinluo group had an obviously decreased carotid IMT after treatment (**Table 4**, $P < 0.01$). Additionally, the major diameter of the plaques and the plaque score decreased considerably (**Table 4**, $P < 0.01$). No significant differences were found in carotid IMT and the number of vulnerable and stable plaques after treatment (Supplemental Tables 2, 3, 4, $P > 0.05$). In summary, CVUS results suggest that the combination of tongxinluo, atorvastatin, and external ultrasound therapy achieved much better effects than any other groups.

Blood lipid levels

Further comparing treatment effects between different groups, blood lipid levels were measured. There was a significant decline in serum levels of TC, TG, and LDL-C after treatment in group A, compared with group B and group C. HDL-C levels increased significantly in group A after treatment, compared with group B and group C (**Table 5**, $P < 0.01$). Lipid levels of group B and group C also differed significantly before and after treatment ($P < 0.01$). The extent of the decline of lipid levels was not significantly different between group B and group C after treatment (Supplemental Tables 5, 6, 7, 8, $P > 0.05$). Current results demonstrate that group A had better therapeutic effects.

Discussion

AS is an important risk factor of cardiovascular and cerebrovascular events in hypertensive patients. It has been confirmed that lipid-lowering therapy could reduce incidence of ischemic cardiovascular and cerebrovascular events in hypertensive patients [12]. In recent years, some studies have suggested that unstable plaques may contribute to cardiovascular events in hypertensive patients [13]. It has been reported that nearly 68% of ischemic cerebrovascular disease showed varying degrees of carotid atherosclerotic plaque [14]. The National Institute of Neurological Disease and Cerebral Infarction suggested that 23% of ischemic cerebrovascular disease is caused by carotid artery disease. Carotid atherosclerotic plaques are mainly composed of lipids and tissue fragments of fibrous caps. Vulnerable plaques have been closely associated with a higher risk of cardiovascular diseases, leading to thrombosis or even ischemic infarction [5, 6]. Therefore, prevention of CAS plaque is an important measure in reducing the risk of cerebrovascular diseases.

Atorvastatin is an inhibitor of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase. It is generally used to lower serum levels of TC, TG, and LDL-C, while raising levels of HDL-C.

Table 2. Changes of length and thickness of fat plaque in the four groups after treatment

		Research group (n = 82)	Atorvastatin group (n = 80)	Tongxinluo group (n = 82)	Control group (n = 80)	F	P
Length (mm)	Initial length	4.69al le	4.76 ± 1.26	4.78 ± 1.47	4.71 ± 1.84	46.37	< 0.001
	After treatment	3.98m1.26	4.45m1.26	4.42m1.26	4.69 ± 1.92		
Thickness (mm)	Initial thickness	1.72kness	1.75 ± 0.28	1.73 ± 0.56	1.75 ± 0.61	43.32	< 0.001
	After treatment	1,30t0.28	1.69 ± 0.42	1.6769 ± 0.	1.71 ± 0.62		
IMT	Before treatment	1.121e tre	1.105e tre	1.113e0.32	1.114 ± 0.34	13.78	< 0.001
	After treatment	0.983 0.187	1.089 0.18	1.096 0.18	1.110 ± 0.28		

Table 3. Comparison of carotid plaque before and 6 months after treatment among different groups

Prior treatment	Vulnerable plaque (%)	Stable plaque (%)	χ^2	P^*
Control group	81 (68.1)	38 (31.9)	0.601	0.896
Research group	86 (67.2)	42 (32.8)		
Tongxinluo group	89 (68.5)	41 (31.5)		
Atorvastatin group	83 (64.3)	46 (35.7)		
Post treatment	Vulnerable plaque (%)	Stable plaque (%)	χ^2	P^*
Control group	78 (65.5)	41 (34.5)	49.981	0.001
Research group	35 (27.3)	93 (72.7)		
Tongxinluo group	40 (30.8)	90 (69.2)		
Atorvastatin group	40 (31.0)	89 (69.0)		

Note: *Compared with the control group.

Table 4. The number and nature of carotid plaque before and 6 months after treatment

		Vulnerable plaque (%)	Stable plaque (%)	χ^2	P
Research group	Prior treatment	86 (67.2)	42 (32.8)	40.763	< 0.001
	Post treatment	35 (27.3)	93 (72.7)		
Tongxinluo group	Prior treatment	89 (68.5)	41 (31.5)	36.941	< 0.001
	Post treatment	40 (30.8)	90 (69.2)		
Atorvastatin group	Prior treatment	83 (64.3)	46 (35.7)	28.729	< 0.001
	Post treatment	40 (31.0)	89 (69.0)		
Control group	Prior treatment	81 (68.1)	38 (31.9)	0.171	0.680
	Post treatment	78 (65.5)	41 (34.5)		

Atorvastatin can effectively reduce cholesterol synthesis and absorption, facilitate LDL clearance, reduce the lipid core, and enhance its stability. Moreover, atorvastatin can protect the vascular endothelium, reducing infiltration of inflammatory cells inside the plaque, alleviating inflammatory response, increasing synthesis, and reducing decomposition of the matrix inside the plaque. Additionally, atorvastatin removes free radicals and inhibits oxidative modification of LDL, reducing the production of foam cells and relieving damage of oxidative LDL (ox-LDL) to the endothelial cells [15-18].

Tongxinluo capsules are a Chinese patent medicine. They can be used to reduce lipid levels, dilute vessels, and protect the vascular endothelium. It contains ginseng, leech, scorpion, ground beetle, centipede, cicada slough, red peony root, and borneol. Some studies have shown that tongxinluo has anti-inflammatory, anti-oxidative, lipid-lowering, and plaque-removing effects [19-22]. It can reduce levels of macrophages inside the plaque by increasing the acoustic density of plaque and the thickness of the fibrous caps. Tongxinluo can stabilize and reverse plaque by reducing the plaque area and plaque load. It reduces lipid levels in the plaque, while increasing collagen levels [9]. In the terminology of Traditional Chinese Medicine, tongxinluo can benefit Qi for activating blood circulation and remove obstruction in channels, thus relieving pain. In this study, compared with the control group, the tongxinluo group showed better effects, suggesting that tongxinluo can effectively interfere with carotid atherosclerotic plaque occurrence and development. The mechanisms may be that tongxinluo upregulates expression of ATP in carotid artery plaques by binding adenosine triphosphate and translo-

Table 5. Blood lipid changes before and 6 months after treatment

	Research group (n = 82)	Atorvastatin group (n = 80)	Tongxinluo group (n = 82)	Control group (n = 80)	F	P
TG[1] (mmol/L)	-1.32 ± 0.32	-1.01 ± 0.35	-1.02 ± 0.31	-0.32 ± 0.30	140.82	< 0.001
TC[2] (mmol/L)	-2.11 ± 0.51	-1.22 ± 0.48	-1.31 ± 0.43	-0.13 ± 0.21	296.59	< 0.001
HDL-C[3] (mmol/L)	0.36 ± 0.31	0.18 ± 0.24	0.16 ± 0.28	0.35 ± 0.29	11.78	< 0.001
LDL-C[4] (mmol/L)	-1.12 ± 0.44	-0.81 ± 0.41	-0.82 ± 0.45	-0.13 ± 0.26	89.27	< 0.001

[1]TG: triglyceride; [2]TC Total cholesterol; [3]HDL-C: high-density lipoprotein cholesterol; [4]LDL-C: low-density lipoprotein cholesterol.

Table 6. Adverse events in the four groups after 6 months of treatment

	Research group (n = 82)	Tongxinluo group (n = 82)	Atorvastatin group (n = 80)	Control group (n = 80)	P
Liver-dysfunction (%)	0 (0.00)	8 (9.75)	0 (0.00)	0 (0.00)	< 0.001
Gastrointestinal reaction (%)	2 (2.43)	6 (7.31)	2 (2.50)	1 (1.25)	
Muscle pain (%)	0 (0.00)	4 (4.87)	0 (0.00)	0 (0.00)	
Joint pain (%)	0 (0.00)	2 (2.43)	1 (1.25)	0 (0.00)	
Adverse events (%)	2 (2.43)	20 (24.39)	3 (3.75)	1 (1.25)	

cating Al and retinoic acid X receptors and accelerating the flow of cholesterol from the cells, reducing the progression of atherosclerosis [23-26].

The use of ultrasound treatment for strokes is mainly because it has a mechanical warming effect on the tissue cells, as well as physical and chemical effects. These are achieved through the skull after a direct role in brain cells, causing material movement within the organization. Thus, ion and colloid permeability are increased. Expansion of cerebral blood vessels, relief of spasms, reduction of vascular resistance, increased cerebral blood flow, and promotion of the formation of brain tissue collateral circulation may be achieved. These improve cerebral ischemia and hypoxia, thereby promoting the repair of lesions. Activation in the inhibition of brain cells improves the metabolism of substances and enzyme activity. Through the nerve cell reflex effects caused by distant parts of the nerve tissue changes in function, regulating vascular relaxation and contraction reaction [27, 28]. In addition, ultrasound treatment can stimulate the release of mast cells in the superoxide factor and promote the accumulation of phagocytic cells to the lesion. Efficacy levels may be related to the improvement of phagocytic cells [29, 30].

The combined use of oral atorvastatin, tongxinluo, and external ultrasound therapy has achieved significant lipid-lowering effects and satisfactory removal of plaques. Follow-up observations of 82 cases indicated that lipid levels decreased continuously, with an increase in serum levels of HDL-C, a reduction in carotid IMT, and a significant transformation of vulnerable plaque into stable plaque. Moreover, plaques completely disappeared in 8 cases. In addition, 20 patients in the atorvastatin group had muscle-joint pain, abnormal liver function, and gastrointestinal reactions (**Table 6**). Incidence of adverse events was as high as 24%. Tongxinluo combined with atorvastatin can reduce normal doses of atorvastatin, as well as incidence of adverse events.

Disclosure of conflict of interest

None.

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References

[1] Hua Y, Zheng Y, Ling C, Duan C, Zhang L, Wang L, Liu Y and Zhou Y. Correlation between atherosclerosis risk factors and carotid stenosis and ischemic stroke. Chinese Journal of CereBrovascular Diseases 2004; 12: 69-72.

[2] Yamagami H, Kitagawa K, Nagai Y, Hougaku H, Sakaguchi M, Kuwabara K, Kondo K, Masuyama T, Matsumoto M and Hori M. Higher

levels of inter-leukin-6 are associated with lower echogenicity of carotid artery plaques. Stroke 2004; 35: 677-681.
[3] Liu L, Qian YQ, Liu JR, Zhang J, Zhou XD, Li J and Li YK. Study on intima-media thickness of the carotid and femoral arteries and endothelium-dependent dilation of the brachial artery in normal subjects. China Ultrasound Med 2005; 21: 838-840.
[4] Crouse JR, Harpold GH, Kahl FR, Toole JF and McKinney WM. Evaluation of a scoring system for extracranial carotid atherosclerosis extent with B-mode ultrasound. Stroke 1986; 17: 270-5.
[5] Waltenberger J. The pathophysiological basis of unstable coronary syndromes. Herz 2001; 26: 2-8.
[6] Galis ZS and Khatri JJ. Matrix metalloproteinase in vascularre modeling and thermogenesis: the good, the bad, and the ugly. Circ Res 2002; 90: 251-262.
[7] Gao T, Zhang Z, Yu W, Zhang Z and Wang Y. Atherosclerotic carotid vulnerable plaque and subsequent stroke: a high-resolution MRI study. Cerebrovasc Dis 2009; 27: 345-52.
[8] Pourcelot L, Tranquart F, De Bray JM, Philippot M, Bonithon MC, Salez F. Ultrasound characterization and quantification of carotid atherosclerosis lesions. Minerva Cardioangiol 1999; 47: 15-24.
[9] Chinese society for neuroscience and Chinese society of department of neurosurgery. Diagnostic criteria for various types of cerebrovascular diseases. Chinese Journal of Neurology 1996; 29: 379-380.
[10] Walter DH, Fichtlscherer S, Britten MB, Auch-Schwelk W, Schächinger V and Zeiher AM. Benefits of immediate initiation of statin therapy following successful coronary stent implantation in patients with stable and unstable angina pectoris and q-wave acute myocardial in farction. Am J Cardiol 2002; 89: 1-6.
[11] Wang H, Yu W, Li Y, Li JX and Jia G. In the atorvastatin and cerebral ultrasonic therapy on fatty plaques in carotid artery intervention. Journal of Military Medicine 2011; 12: 944-946.
[12] Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National cholesterol education program adult treatment panel III guidelines. Circulation 2004; 110: 67-71.
[13] Roivainen M, Viik-Kajander M, Palosuo T, Toivanen P, Leinonen M, Saikku P, Tenkanen L, Manninen V, Hovi T and Mänttäri M. Infection, inflammation, and the risk of coronary heart disease. Circulation 2000; 101: 252-257.
[14] Palak J, Shemansk L and O Leary DH. Relationship between incident stroke and severity of internal carotid stenosis. Circlation 1994; 90: 1399-1404.
[15] Rutishauser J. The role of statins in clinical medicine--LDL--cholesterol lowering and beyond. Swiss Med Wkly 2006; 136: 41-9.
[16] Castilla Guerra L, del Carmen Fernández Moreno M, López Chozas JM and Jiménez Hernández MD. Statins in stroke prevention: what an internist should know. Eur J hterm Med 2008; 19: 89-91.
[17] Amarenco P, Labreuche J, Lavallée P and Touboul PJ. Statins in stroke prevention and carotid atherosclerosis. Stroke 2004; 35: 2902-2909.
[18] Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, Zeiher A, Chaitman BR, Leslie S, Stern T; Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA 2001; 285: 1711-1718.
[19] Li Z, Yang YJ, Qin XW, Ruan YM, Chen X, Meng L, Zhang HD. Effects of Tongxinluo and Simvastatin on the stabilization of vulnerable atherosclerotic plaques of aorta in aortic atherosclerosis and molecular mechanism thereof: a comparative study with rabbits. Zhonghua Yi Xue Za Zhi 2006; 86: 3146-3150.
[20] Liu JX, Shang XH and Wang G. Effect of tongxinluo capsule on experimental myocardial ischemia, arrhythmia and hyperlipidemia. Zhongguo Zhong Xi Yi Jie He Za Zhi 1997; 17: 425-428.
[21] Wu YL, You JH, Yuan GQ, Liang JQ, Jia ZH, Liu KJ and Wei C. The effects of tongxinluo supermicro powder on nuclear factor-kappaB, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 expression in aorta of rabbits fed with high-lipid diet. Zhonghua Xin Xue Guan Bing Za Zhi 2007; 35: 271-274.
[22] Zhang L, Wu Y, Jia Z, Zhang Y, Shen HY and Wang XL. Protective effects of a compound herbal extract (Tong Xin Luo) on free fatty acid induced endothelial injury: implications of antioxidant system. BMC Complement Altem Med 2008; 8: 39.
[23] Zhang HT, Yang YJ and Cheng YT. Effect of tongxinluo on mini-swine cytokines and myocardial no-reflow in early reperfusion of acute myocardial infarction. Zhongguo Zhong Xi Yi Jie He Za Zhi 2009; 29: 821-824.
[24] Zhang L, Liu Y, Lu XT, Wu YL, Zhang C, Ji XP, Wang R, Liu CX, Feng JB, Jiang H, Xu XS, Zhao YX, Zhang Y. Traditional Chinese medication

Tongxinluo dose-dependently enhances stability of vulnerable plaques: a comparison with a high dose simvastatin therapy. Am J Physiol Heart Circ Physiol 2009; 297: H2004-14.

[25] Liu H, Yang Q and Miao W. ATP binding transport swivel Al and carotid atherosclerotic plaque. Chinese Journal of Neurology 2007; 40: 187.

[26] Barsotti S, Ruf MW, Hotop H. Clear experimental evidence for p-wave attachment-threshold behavior in electron attachment to chlorine molecules. Phys Rev Lett 2002; 89: 083201.

[27] Boldyrev S, Nordlund A and Padoan P. Supersonic turbulence and structure of interstellar molecular clouds. Phys Rev Lett 2002; 89: 031102.

[28] Kitchen WH, Ford GW and Rickards AL. Five-year outcome of infants of birth weight 500-1 500 grams: relationship with neonatal ultrasound data. Arn J Perinatol 1990; 7: 60-65.

[29] Du B and Zhao G. Clinical observation on the treatment of cerebral infarction by ultrasound-medium frequency electrotherapy. Chinese Journal of Physical Therapy 1996; 9: 223-226.

[30] Harpaz D, Chen X and Francis CW. Ultrasound auelerates urokinase in duced thrombolysis and reperfusion. Am Heart 1994; 127: 1211-1219.

Supplemental Table 2. Comparison of changes of fat plaque length in four groups after treatment

		Mean difference	Standard error	P	95% CI	
					Lower	Upper
Control group	Research group	1.09	0.15	< 0.01	0.80	1.38
	Atorvastatin group	0.48	0.16	< 0.05	0.17	0.79
	Tongxinluo group	0.53	0.15	< 0.05	0.24	0.82
Research group	Control group	-1.09	0.15	< 0.01	-1.38	-0.80
	Atorvastatin group	-0.61	0.15	< 0.05	-0.90	-0.32
	Tongxinluo group	-0.56	0.15	< 0.05	-0.85	-0.27
Atorvastatin group	Control group	-0.48	0.16	< 0.05	-0.79	-0.17
	Research group	0.61	0.15	< 0.05	0.32	0.90
	Tongxinluo group	0.05	0.15	> 0.05	-0.24	0.34
Tongxinluo group	Control group	-0.53	0.15	< 0.05	-0.82	-0.24
	Research group	0.56	0.15	< 0.05	0.27	0.85
	Atorvastatin group	-0.05	0.15	> 0.05	-0.34	0.24

Supplemental Table 3. Comparison of changes of fat plaque thickness in four groups after treatment

		Mean difference	Standard error	P	95% CI	
					Lower	Upper
Control group	Research group	0.40	0.04	< 0.01	0.32	0.48
	Atorvastatin group	0.15	0.04	< 0.01	0.07	0.23
	Tongxinluo group	0.17	0.04	< 0.01	0.09	0.25
Research group	Control group	-0.40	0.04	< 0.01	-0.48	-0.32
	Atorvastatin group	-0.25	0.04	< 0.01	-0.33	-0.17
	Tongxinluo group	-0.23	0.04	< 0.01	-0.31	-0.15
Atorvastatin group	Control group	-0.15	0.04	< 0.01	-0.23	-0.07
	Research group	0.25	0.04	< 0.01	0.17	0.33
	Tongxinluo group	0.02	0.04	> 0.05	-0.06	0.10
Tongxinluo group	Control group	-0.17	0.04	< 0.01	-0.25	-0.09
	Research group	0.23	0.04	< 0.01	0.15	0.31
	Atorvastatin group	-0.02	0.04	> 0.05	-0.10	0.06

Supplemental Table 4. The number and nature of carotid plaques in four groups 6 months after treatment

	Research group	Atorvastatin group	Tongxinluo group	Control group	*P*
Vulnerable plaque (%)	35 (27.3)*	40 (30.8)*	40 (31.0)*	78 (65.5)	0.000
Stable plaque (%)	93 (72.7)	90 (69.2)	89 (69.0)	41 (34.5)	

*Compared with the control group $p < 0.01$.

Supplemental Table 5. The comparison of TG changes in the four groups before and after treatment for 6 months

		Mean difference	Standard error	P	95% CI	
					Lower	Upper
Control group	Research group	1.00	0.04	< 0.01	0.93	1.07
	Atorvastatin group	0.69	0.04	< 0.01	0.62	0.76
	Tongxinluo group	0.70	0.04	< 0.01	0.63	0.77
Research group	Control group	-1.00	0.04	< 0.01	-1.07	-0.93
	Atorvastatin group	-0.31	0.04	< 0.01	-0.38	-0.24
	Tongxinluo group	-0.30	0.04	< 0.01	-0.37	-0.23
Atorvastatin group	Control group	-0.69	0.04	< 0.01	-0.76	-0.62
	Research group	0.31	0.04	< 0.01	0.24	0.38
	Tongxinluo group	-0.01	0.04	> 0.05	-0.08	0.06
Tongxinluo group	Control group	-0.70	0.04	< 0.01	-0.77	-0.63
	Research group	0.30	0.04	< 0.01	0.23	0.37
	Atorvastatin group	0.01	0.04	> 0.05	-0.06	0.08

Supplemental Table 6. The comparison of TC changes in the four groups before and after treatment for 6 months

		Mean difference	Standard error	P	95% CI	
					Lower	Upper
Control group	Research group	1.98	0.05	< 0.01	1.88	2.08
	Atorvastatin group	1.09	0.05	< 0.01	0.99	1.19
	Tongxinluo group	1.88	0.05	< 0.01	1.78	1.98
Research group	Control group	-1.98	0.05	< 0.01	-2.08	-1.88
	Atorvastatin group	-0.89	0.05	< 0.01	-0.99	-0.79
	Tongxinluo group	-0.80	0.05	< 0.01	-0.90	-0.70
Atorvastatin group	Control group	-1.09	0.05	< 0.01	-1.19	-0.99
	Research group	0.89	0.05	< 0.01	0.79	0.99
	Tongxinluo group	0.09	0.05	> 0.05	-0.01	0.19
Tongxinluo group	Control group	-1.88	0.05	< 0.01	-1.98	-1.78
	Research group	0.80	0.05	< 0.01	0.70	0.90
	Atorvastatin group	-0.09	0.05	> 0.05	-0.19	0.01

Supplemental Table 7. The comparison of HDL-C changes in the four groups before and after treatment for 6 months

		Mean difference	Standard error	P	95% CI	
					Lower	Upper
Control group	Research group	0.18	0.03	< 0.01	0.16	0.05
	Atorvastatin group	0.17	0.03	< 0.01	0.11	0.23
	Tongxinluo group	0.19	0.03	< 0.01	0.13	0.25
Research group	Control group	0.18	0.03	< 0.01	0.14	0.07
	Atorvastatin group	0.18	0.03	< 0.01	0.12	0.24
	Tongxinluo group	0.20	0.03	< 0.01	0.14	0.26
Atorvastatin group	Control group	-0.17	0.03	< 0.01	-0.23	-0.11
	Research group	-0.18	0.03	< 0.01	-0.24	-0.12
	Tongxinluo group	0.02	0.03	> 0.05	-0.04	0.08
Tongxinluo group	Control group	-0.19	0.03	< 0.01	-0.25	-0.13
	Research group	-0.20	0.03	< 0.01	-0.26	-0.14
	Atorvastatin group	-0.02	0.03	> 0.05	-0.08	0.04

Supplemental Table 8. The comparison of LDL-C changes in the four groups before and after treatment for 6 months

		Mean difference	Standard error	P	95% CI	
					Lower	Upper
Control group	Research group	0.99	0.04	< 0.01	0.91	1.07
	Atorvastatin group	0.68	0.04	< 0.01	0.60	0.76
	Tongxinluo group	0.69	0.04	< 0.01	0.61	0.77
Research group	Control group	-0.99	0.04	< 0.01	-1.07	-0.91
	Atorvastatin group	-0.31	0.04	< 0.01	-0.39	-0.23
	Tongxinluo group	-0.30	0.04	< 0.01	-0.38	-0.22
Atorvastatin group	Control group	-0.68	0.04	< 0.01	-0.76	-0.60
	Research group	0.31	0.04	< 0.01	0.23	0.39
	Tongxinluo group	0.01	0.04	> 0.05	-0.07	0.09
Tongxinluo group	Control group	-0.69	0.04	< 0.01	-0.77	-0.61
	Research group	0.30	0.04	< 0.01	0.22	0.38
	Atorvastatin group	-0.01	0.04	> 0.05	-0.09	0.07