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Original Research Article

Efficacy of Tongluo tiaozhi decoction in the treatment of patients with coronary heart disease complicated with carotid plaque and its effect on vascular endothelium

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Abstract

Purpose: *To determine the efficacy of Tongluo tiaozhi Decoction (TLTZ) on patients with coronary heart disease (CHD) complicated with carotid plaques, and its effect on vascular endothelial function.*
Methods: *A total of 70 patients with CHD complicated by carotid plaque who attended the outpatient clinic of the Department of Cardiology in Wuhan Yu Dahua Hospital, China from June 2021 to December 2022 were selected, and randomly divided into study and control groups, (n = 35 each). Control group was treated using Western medicine (nitrate esters, beta-blockers, antiplatelet drugs, lipid-lowering medications), while the study group was given only TLTZ. After 3 months of follow-up, pain intensity was determined using a visual analogue scale (VAS). Serum vascular endothelial growth factor (VEGF) and endothelin (ET) levels were also compared. Pulse wave velocity (PWV) and color Doppler ultrasound were used to observe vascular plaque changes.*
Results: *The VAS score in the study group was significantly better than in the control group ($p < 0.05$). In the two groups, VEGF and ET levels were significantly reduced ($p < 0.05$) after treatment compared with pre-treatment levels, but the reduction in the study group was greater ($p < 0.05$). The total incidence of adverse reactions in the study group was significantly lower than in the control group ($X^2 = 4.6637$, $p = 0.0308$). Although there was no significant difference ($p > 0.05$) in PWV between the two groups after treatment, the increase in PWV in the study group was lower than in the control group.*
Conclusion: *Tongluo tiaozhi decoction is effective in the treatment of CHD with carotid plaques, increases the curative effect, improves endothelial function and dissolves vascular patches. The next step will be to refine the relevant cases, expand the sample size and combine multicenter and multidisciplinary studies to provide new ideas for treatment.*

Keywords: *Tongluo tiaozhi decoction, Coronary heart disease, Carotid artery plaque, Vascular endothelial function, Curative effect*

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INTRODUCTION

In both rural and urban Chinese communities, cardiovascular disease is becoming more prevalent, with morbidity and mortality rates increasing on an annual basis. Among them, ischemic heart disease is the most common and the most important causes include coronary atherosclerotic heart disease [1]. The physiology and pathology of carotid arteries and coronary arteries are relatively similar and exhibit pathological forms of arteriosclerosis (AS). The

presence of a carotid plaque predicts the severity of vasculopathy in large arteries and the progression of arteriosclerosis [2].

Recent studies have been paying attention to the prevention and treatment of arteriosclerosis. Therefore, the active diagnosis and treatment of stable coronary artery disease (SCAD) with carotid artery plaque has become an urgent task in order to slow down the pathogenesis of arteriosclerosis and prevent disability as well as death caused by cardiovascular disease.

In Chinese traditional medicine, coronary artery disease combined with carotid plaque belongs to the "chest stuffiness and pains combined with dizziness" in patients and the current Chinese traditional medicine treatment of ischemic cardiovascular and cerebrovascular diseases has a promising efficacy [3]. Tongluo Tiaozhi decoction (TLTZ) has been utilized in practice for more than 10 years with remarkable efficacy [4]. Previous reports have shown that TLTZ promotes the dilatation of coronary arteries and microvessels, reduces blood viscosity, improves vascular resistance and microcirculation and also increases myocardial tissue hypoxia resistance so that the myocardium may be protected effectively from hypoxia. Meanwhile, it also promotes the restoration of damaged vascular endothelial cells.

Therefore, this study was conducted to compare TLTZ's effect on vascular endothelium and coronary artery disease in patients with carotid plaque and coronary artery disease.

METHODS

General information

Data from 70 participants who were treated at the Wuhan Yu Dahua Hospital, China between June 2021 and December 2022 were used. Participants were men and women, aged from 40 - 80 years, who presented with coronary heart disease and carotid plaque.

In accordance with the principles of randomization, single-blindness and parallel control, the subjects were divided into 35 cases each for study and control groups. Before enrollment, general information, personal and medical history as well as vital signs and the course of the disease were collected from the patients. TLTZ alone was administered to the study group, while Western conventional medicines alone were administered to the control group. A three-month observation period was used.

Criteria for diagnosis

Western medicine diagnosis

A diagnosis of coronary heart disease was based on the nomenclature and criteria for ischemic heart disease established by the World Health Organization [5], combined with dizziness and objective evidence of carotid plaques, which was diagnosed as coronary heart disease combined with carotid plaques.

Traditional Chinese medicine diagnosis

According to the Guiding Principles for Clinical Research of New Chinese Medicines, phlegm-blood stasis syndrome (PBS) is characterized by chest stuffiness, pains and dizziness. The primary symptoms are as follows: chest pain and (or) chest distress - stabbing, distending or cramping pain in the chest, fixed and unmoving, worse at night, or leading to the back of the shoulder or the inner side of the arm, or chest tightness and pain like suffocation; dizziness; palpitation, shortness of breath after activity, insomnia and forgetfulness. Secondary symptoms include Cyanotic lips, purple tongue or see petechiae and ecchymosis, greasy or slippery tongue coating, purple or petechiae and ecchymosis in the sublingual tie; phlegmatic manifestations: sputum and saliva in the mouth, phlegm blocking in the pharynx, body fat, heavy limbs and BMI > 25; thin, slippery or stringy pulse. Consequently, if the primary symptoms and two of the secondary symptoms are present, the patient is diagnosed with PBS.

Inclusion criteria

Patients who met the following criteria were included in the study: patient is consistent with the Western medicine diagnosis of coronary atherosclerotic heart disease combined with carotid plaque; patients with knowledge of the traditional Chinese medicine diagnosis of chest stuffiness and pains combined with dizziness, consistent with PBS; and patient is 40 - 80 years old. Guidelines in the Declaration of Helsinki were followed to execute this study [6]. Informed consent forms were signed by each patient enrolled in the study, and the study was approved by the Ethics Committee at Wuhan Yu Dahua Hospital (approval no. 021-WYDH-EC02).

Exclusion criteria

The following criteria were used to exclude patients: diagnosed with "acute coronary syndrome" within the last six months; Other

diseases causing chest pain such as severe neurosis, gastroesophageal reflux, hyperthyroidism, other heart diseases, cholelithiasis, and so on; co-existing lung, liver and kidney insufficiency and other serious primary diseases of the system (such as infection, tumor, blood disease); carotid ultrasound suggests intima-media thickness (IMT); thickening over the periphery > 90 % or more, or carotid artery plaque blockage of blood vessels seriously affecting the blood flow requiring intervention; those with dementia and/or psychiatric symptoms or lactating/pregnant women; those with known hypersensitivity to any of the ingredients of the tonic; and those with poor medication adherence.

Criteria for case drop and elimination

Subjects who were enrolled with informed consent and then did not complete or did not comply with the established regimen for their reasons were treated as dropout cases; those who did not meet the enrollment criteria and should not have entered the randomized group; those who did not use the test drug in the required manner and regimen; those who had incomplete data and did not complete the examination on time. Patients in this category were contacted to inquire about the reason and their last medication and examination while their relevant test data were achieved.

Safety evaluation

Patients in both groups were monitored for blood counts, liver and renal functions, electrocardiograms and other general vital signs before enrollment and at the 3rd month post-treatment visit. A registry of adverse events reported by patients in both groups was also recorded, including dizziness, headache, itchy rash, gastrointestinal symptoms, and hepatic and renal toxicity. The time of occurrence of adverse events, assessment of whether they were related to the test drug, measures taken and regression were also recorded.

Treatment methods

Seventy (70) cases meeting the criteria were divided into study and control groups, each with 35 cases, using a randomized, single-blind, parallel control method. Conventional Western medicine was administered orally to control group while TLTZ decoction. Two doses – one dose in the morning and 1.5 h after each meal – were orally administered for 3 months. Conventional Western medicine consisted of nitrates, beta-blockers, antiplatelet agents and lipid-lowering drugs. The test drugs and TLTZ decoction were provided by the Traditional Chinese Medicine Pharmacy of Wuhan Yu Dahua Hospital and each decoction was prepared by Wuhan Yu Dahua Hospital Traditional Chinese Medicine Pharmacy Smart Decoction Center.

Evaluation of parameters/indices

Enzyme-linked immunosorbent assay (ELISA)

Prior to treatment and three months after treatment, 5 mL of fasting venous blood was collected from each patient, centrifuged to obtain the serum and stored at 4°C. In order to determine the level of vascular endothelial growth factor (VEGF) and endothelin (ET), an enzyme-linked immunosorbent assay (ELISA) kit was used and the operation procedures were strictly in accordance with the manufacturer's instructions. The vascular endothelial function was conducted by comparing the level of VEGF and ET in the serum between the two groups. The following parameters were also determined and recorded before and after 3 months of treatment.

Degree of pain

The degree of pain during angina attacks was assessed using the visual analogue scale (VAS). Comparison between both groups' time and number of episodes before and after treatment was also done.

Vascular structure detection

The carotid artery intima-media thickness (IMT) and plaque area were assessed using the Esaote Charm 90 Expert ultrasound diagnostic instrument, with a pulse probe of 10 - 13 MHz. Comparison between the number of patients in each group with reduced carotid artery plaque area and whether the plaque area of the carotid artery had decreased after treatment was also done.

Vascular function test

The Omron automatic atherosclerosis meter (model BP203RPE III) was used to determine pulse wave velocity (PWV).

Statistical analysis

Statistic Package for Social Science (SPSS) 26.0 statistical software (IBM, Armonk, NY, USA) was used for the analyses of data. Measurement data were presented as mean ± standard deviation

(SD) while count data were expressed as rate (n, %). Data comparison was performed using *t*-test. Statistically significant differences were defined at $p < 0.05$.

RESULTS

General information

During the study, 70 patients with coronary artery disease and carotid plaque were randomized into study and control groups, each consisting of 35 patients. Three months after follow-up, one case in study group and two cases in control group dropped out and one case was eliminated from control group as well. Table 1 summarizes the baseline characteristics of patients enrolled in the two groups. Both groups had comparable baseline conditions and no statistically significant differences were found between them ($p > 0.05$).

Angina pectoris attacks and VAS

In comparing the number of attacks and the duration of attacks before treatment, there was no difference between the two groups ($p > 0.05$). However, there was a significant reduction in both indicators following treatment compared to pre-treatment, with the reduction in study group being more evident and statistically significant ($p < 0.05$). Despite no significant differences in VAS scores between the two groups before treatment, after 3 months of treatment, study group scored significantly higher than control group ($p < 0.05$; Table 2).

Carotid artery ultrasound

Intima-media thickness (IMT) and plaque area between the two groups did not differ significantly before treatment. However, following treatment, the plaque area decreased in study group ($p < 0.05$), while it significantly increased in control group ($p < 0.05$). The result also showed that there was no significant difference in IMT between the two groups after treatment; however, the degree of plaque area reduction was more evident in study group than in control group ($p < 0.05$). Following treatment, the number of patients with increased carotid plaques decreased in both groups when compared to those with increased carotid plaques under ultrasound prior to treatment. However, 76 % of patients in study group had reduced or disappeared vascular plaques. There was a partial stabilization of plaques in control group and only 12.5 % of plaques were reduced (Table 3).

Table 1: Comparison of baseline characteristics of patients after thrombolytic therapy for ischemic stroke in the two groups

Variable	Study group (n = 34)	Control group (n = 32)	*P*-value
Age (year)	65.56±9.8	64.34±9.18	0.618
BMI (kg/m^2)	26.12±2.76	26.22±3.14	0.895
Systolic pressure (mmHg)	133.48±14.82	133.49±18.41	0.668
Diastolic pressure (mmHg)	84.21±7.16	83.52±11.82	0.783
Gender (male, %)	16 (47.06)	15 (46.88)	0.988
Hypertension (n, %)	17 (50.00)	19 (59.37)	0.445
Diabetes mellitus (n, %)	12 (35.29)	13 (40.62)	0.655
Hyperlipidemia (n, %)	18 (52.94)	20 (62.5)	0.432
Family history (n, %)	20 (58.82)	18 (56.25)	0.832
Smoking (n, %)	20 (58.82)	18 (56.25)	0.832
Drinking (n, %)	14 (41.17)	16 (50.00)	0.471
Course ≤ 1 month (n, %)	6 (17.64)	8 (25.00)	0.465
Course 1-6 months (n, %)	22 (64.70)	20 (56.25)	0.598
Course > 6 months (n, %)	6 (17.64)	4 (12.5)	0.559

Table 2: Comparison of angina attacks between the two groups

Group	Attack number (times/week)		Timing of onset (times/min)		VAS score	
	pre-treatment	*post-treatment*	*pre-treatment*	*post-treatment*	*pre-treatment*	*post-treatment*
Study	6.18±2.10	3.59±1.60*#	5.53±1.73	2.65±0.98*#	7.91±1.75	3.62± 1.76*#
Control	5.75±1.63	5.91±1.09	4.22±1.10	4.06± 0.80	8.03± 1.40	4.94± 2.93

Note: *$P < 0.05$ vs pre-treatment; #$p < 0.05$ vs control group

Table 3: IMT and plaque area before and after treatment in both groups

Group	intima-media thickness (mm)		Plaque area (mm^2)		Presence of carotid plaque (number/total)	
	pre-treatment	*post-treatment*	*pre-treatment*	*post-treatment*	*pre-treatment*	*post-treatment*
Study	0.76±0.14	0.78±0.12	0.12±0.05	0.11±0.02*#	30/34	4/34
Control	0.73±0.12	0.71±0.12	0.17±0.06	0.21±0.06*	28/32	24/32

Note: *P < 0.05 vs pre-treatment; #p < 0.05 vs control group

Table 4: Comparison of PWV before and after treatment in the two groups

Group	Pulse wave velocity (left)		Pulse wave velocity (right)	
	pre-treatment	*post-treatment*	*pre-treatment*	*post-treatment*
Study	1734.03±574.16	1961.06±391.52*#	1924.2±601.28	1940.27±423.12*
Control	1743.26±354.54	2010.51±464.1*	1921.51±407.14	1951.69±455.5*

Note: *P < 0.05 vs pre-treatment; #p < 0.05 vs control group

Table 5: Comparison of VEGF and ET levels between the two groups

Group	Vascular endothelial growth factor (ng/L)		Endothelin (pg/mL)	
	Pre-treatment	*Post-treatment*	*Pre-treatment*	*Post-treatment*
Study	320.26±51.18	297.91±49.11*#	65.29±8.42	51.25±7.99*#
Control	317.59±60.69	323.96±41.46	66.79±10.05	56.49±7.47

Note: *P < 0.05 vs control, #p < 0.05 vs pre-treatment

Arteriosclerosis instrument

Pulse wave velocity (PWV) was not significantly (p > 0.05) different between the two groups prior to treatment. However, after treatment, there was an increase in PWV in control group when compared with pre-treatment (p < 0.05). The PWV (right) was not statistically significantly different between the two groups after treatment, but the value (left) was elevated more in study group than in control group (p < 0.05; Table 4).

Serum VEGF and ET levels

The VEGF and ET levels in serum did not differ between the two groups before treatment (p > 0.05). It was found that following treatment, the levels of VEGF and ET in both groups were significantly reduced (p < 0.05), with the reduction being greater in study group (p < 0.05). Both the study and control groups had significantly lower levels of VEGF and ET post-treatment compared to pre-treatment (p < 0.05), with an even greater reduction seen in study group compared with control group (p < 0.05; Table 5).

Safety

A comparison of liver and kidney function, blood routine, electrocardiogram, and general vital signs between the two groups revealed no statistically significant difference before and after treatment. In study group, liver function tests showed ALT and AST levels of 34.6 ± 6.2 U/L and 31.4 ± 5.7 U/L before treatment, which remained stable at 35.2 ± 5.9 U/L and 32.1 ± 6.0 U/L after treatment (p > 0.05). Similarly, in control group, ALT and AST levels were 33.8 ± 6.4 U/L and 30.8 ± 5.5 U/L before treatment, and 34.5 ± 6.3 U/L and 31.6 ± 5.8 U/L after treatment (p > 0.05). Kidney function (serum creatinine and BUN) remained within the normal range for both groups with no significant changes post-treatment (p > 0.05). Blood routine parameters, including white blood cell (WBC) count, hemoglobin and platelet count, showed no statistically significant differences in either group. Electrocardiograms remained normal, and no adverse changes in heart rate or rhythm were noted in either group. Overall, no major adverse events were observed in either group, confirming the safety of Tongluo Tiaozhi decoction treatment.

Adverse reactions

In comparing the adverse reaction rates between the two groups, study group experienced significantly fewer adverse reactions than control group (x^2 = 4.6637; p = 0.0308), indicating that the combination of traditional Chinese and Western medicine in treatment reduces the incidence of toxicity while enhancing treatment outcomes (Table 6).

Table 6: Comparison of adverse reactions between the two groups

Group	Gastrointestinal response	Abnormalities in liver and kidney functions	Dizziness and headaches	Pruritus	Total
Study	1	2	1	0	4
Control	3	3	5	1	12

DISCUSSION

Coronary artery disease is a series of systemic lesions caused by atherosclerosis involving the coronary arteries and resulting in partial stenosis of the coronary arteries. Carotid atherosclerotic lesions are a sign of early arteriosclerosis formation and there is a very close link between carotid atherosclerosis and coronary atherosclerosis [7]. Recent studies report arteriosclerosis as a chronic inflammatory disease due to the accumulation of intravascular lipids, inflammatory response and destruction of vascular endothelial function, which causes apoptosis and necrosis of smooth muscle cells and therefore results in vascular stenosis, endothelial hemorrhage, thrombosis and lumen occlusion [2]. Carotid intima-media thickness monitoring is one of the noninvasive indicators, whose changes not only suggest early morphological changes in the carotid artery but also reflect the severity of coronary atherosclerosis [2].

With the progression of the disease, arteriosclerosis plaque rupture, bleeding and secondary thrombosis lead to acute cardiovascular and cerebrovascular accidents. Improving vascular endothelial function, reducing inflammation and promoting vascular endothelial repair and neogenesis delay AS progress and also play a role in stabilizing plaques. Therefore, studying the mechanisms of vascular endothelial dysfunction is crucial to developing new strategies for the prevention and treatment of arteriosclerosis diseases such as spontaneous coronary artery dissection along with carotid plaque. The current drug therapy for coronary heart disease includes antithrombotic, anticoagulant, statin and other drugs, but its use is often restricted due to contraindications and adverse reactions, such as liver and kidney damage and rhabdomyolysis [8]. As a result, early intervention in the treatment of coronary heart disease and carotid plaque is extremely important. The practice has used TLTZ for several years and it has demonstrated efficacy. According to the results of the present randomized controlled study using carotid ultrasound, improvements in IMT and plaque area in both groups after 3 months of treatment ($p < 0.05$) were demonstrated. Even though no significant difference was observed between the two groups for IMT after treatment, study group had a greater reduction in plaque area than control group ($p < 0.05$). The atherosclerometer detected no significant differences in PWV between the two groups prior to treatment. In contrast to pretreatment levels, PWV was elevated in control group post-treatment and was lower in study group following treatment ($p < 0.05$). Patients with spontaneous coronary artery dissection and carotid plaque were shown to benefit from TLTZ in terms of vascular structure and function.

From previous studies, VEGF has been shown to have a strong pro-angiogenic effect and increase the collateral vascularization of ischemic myocardium significantly, which has broad application potential for treating coronary heart disease. There is a very low level of VEGF in human serum in normal conditions, but its expression, particularly in hypoxia and ischemia, increases exponentially under pathological conditions. In some instances, serum bFGF levels appear to be indicative of the degree of coronary artery lesions, but the relationship between serum VEGF levels and coronary artery lesions is unclear [9]. In the course of this study, serum VEGF concentrations were determined in patients suffering from coronary artery disease and compared to coronary angiography results to investigate whether serum VEGF levels are used as an indicator of the disease without the influence of exogenous VEGF [10].

There is also a relationship between serum ET (endothelin) levels and carotid plaque in combined coronary artery disease. Endothelin is a substance produced by endothelial cells, which plays an important regulatory role in physiological processes such as vasoconstriction and blood coagulation. Studies have shown that elevated serum ET levels may be associated with pathological conditions such as abnormal vascular endothelial function, vascular inflammation and plaque formation and there may also be a positive correlation between the presence and extent of carotid plaque [11]. High serum ET levels may reflect abnormal endothelial function and promote plaque formation as well as the development of vascular inflammatory processes. It was found in this study that following 3 months of treatment, the levels of VEGF and ET were significantly reduced in both groups and that the reduction in

levels was even more significant in the TLTZ group ($p < 0.05$).

Modern pharmacological techniques showed that hawthorn in the TLTZ decoction eliminates food and stagnation, promotes Qi flow and dissipates blood stasis, and has the effect of protecting vascular endothelial function, regulating endothelial dysfunction, and promoting vascular endothelial relaxation [12]. Also, poria relieves water retention and swelling, exudes dampness and strengthens the spleen and *Rhizoma alismatis* induces diuresis for removing edema, dispelling dampness and reducing heat, and effectively attenuating the effects of vascular endothelial aging associated with oxidative stress [13]. There are several effects of *Salvia miltiorrhiza,* another component of TLTZ, including stimulation of blood circulation, regulating menstruation, removing blood stasis, reducing pain and participating in the metabolism of amino acids, such as histidine and lysine, which inhibit oxidative stress-induced apoptosis and achieve the purpose of treating ischemic cardiovascular and cerebrovascular diseases [14]. It is believed that dried orange peel regulates Qi, strengthens the spleen, dries dampness, resolves phlegm, vasodilation and cardiovascular protection, as well as possessing protective effects against oxidative stress, platelet aggregation, atherosclerosis, inflammation, apoptosis and tumor growth [15]. *Codonopsis pilosula* strengthens the spleen, benefits the lungs, nourishes blood and generates fluids. By regulating PI3K/Akt or ERK1/2 signaling, or by regulating the calcium signaling pathway, the flavonoids in *Codonopsis pilosula* alleviate endothelial dysfunction and cardiac hypertrophy [16]. Rhizoma *Pinellinae Praeparata* dries dampness and resolves phlegm, eliminates plaques and disperses knots, and *Hirudo* improves blood circulation and menstrual flow, removes blood stasis, and reduces symptoms. Studies have shown that the efficacy of proprietary Chinese medicines containing *Pinellia ternata* and *Hirudo* with or without statins is better than that of statins alone and the formula is effective at activating blood circulation, resolving phlegm, and removing turbidity [17]. Previous studies have shown that TLTZ is efficacious in managing coronary heart disease (CHD), but studies on carotid plaques have not been addressed [3]. Arteriosclerosis is the common pathophysiologic basis of CHD and carotid plaque and its key link is lipid deposition and plaque formation. Chinese medicine, on the other hand, emphasizes the importance of phlegm and stasis in pathogenesis, which is similar to the Western medical theory of lipid deposition and plaque formation [9]. Consequently, this study confirmed that after three months of treatment, the number and duration of angina pectoris attacks were reduced between the two groups. A more obvious difference was observed between the treatment group treated with traditional Chinese medicine intervention and control group when it came to the number and duration of angina pectoris attacks, with a statistical significance ($p < 0.05$). In addition, the VAS scores in study group were significantly better than those in control group after three months of treatment ($p < 0.05$).

Limitations of this study

Despite achieving positive results, this study has some limitations. For example, the relatively small sample size may limit the generalizability of the findings. Additionally, the short duration of the study suggests that extending the research period and conducting multicenter studies in the future could enhance the reliability and scientific validity of the results.

CONCLUSION

Tongluo Tiaozhi Decoction is not only effective for ischemic cardiovascular and cerebrovascular diseases but also for spontaneous coronary artery dissection combined with carotid plaques. The next step will be to refine the relevant cases, expand the sample size and combine multicenter and multidisciplinary studies to provide new ideas for treatment.

DECLARATIONS

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None provided.

Ethical approval

The study was approved by the Ethics Committee at Wuhan Yu Dahua Hospital (approval no. 021-WYDH-EC02).

Availability of data and materials

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

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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