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Clinical Efficacy of Tongxinluo Capsules in Vietnamese Patients with Stable Ischemic Heart Disease: An Open-label Clinical Trial

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ABSTRACT

Background: The aim of treatment of stable ischemic heart disease is not only to improve prognosis but also to decrease symptoms and increase the patient's quality of life. Pharmaceutical therapy remains the cornerstone of stable angina treatment, and Tongxinluo is a traditional oriental medicine used in the treatment of ischemic heart disease.

Objective: To evaluate the effectiveness of Tongxinluo for improving angina symptoms and exertion ability in Vietnamese patients.

Methods: This open-label clinical trial was conducted as one branch in 300 Vietnamese patients at Cho Ray Hospital. The diagnosis of stable angina followed the 2013 European Society of Cardiology Guidelines. The patients were supplemented with Tongxinluo at a dose of 6 tablets bid. Patients were reassessed for angina symptoms and any subclinical side effects of the drug at 2 weeks and 6 weeks after initiation of the drug treatment.

Results: Exercise time on rolling mats, metabolic equivalents (METs), and other subclinical indices were decreased significantly after 6 weeks of Tongxinluo administration. Side effects of halitosis, a burning sensation, diarrhea, and headaches were mild and tolerable.

Conclusion: Tongxinluo provides a significant reduction in the frequency, duration, and severity of angina. Tongxinluo was well tolerated by this Vietnamese study population.

Keywords: angina, cardiology, oriental medicine, Tongxinluo, Vietnam.

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INTRODUCTION

Ischemic heart disease is presently one of the leading causes of morbidity and mortality in the world.[1] Current treatments for stable ischemic heart disease are therefore aimed at improving prognosis, but they are also directed toward decreasing symptoms and increasing the patient's quality of life.[2] This disease has a complex pathogenetic mechanism that involves narrowing of the coronary arteries, but many other factors play roles in the pathophysiology of ischemic heart disease. These factors include inflammation, endothelial dysfunction, microchial dysfunction, and disruptions in platelet function, thrombosis, and vasomotor function and have led to the new solar system model of coronary artery disease.[3]

The Euro Heart Survey results, based on the analysis of 3,779 patients with stable angina, confirmed the benefits of the use of angina medications in patients undergoing coronary revascularization. Only 3% of these patients did not use angina medications, while 55% used two types and 20% needed more than two.[4] Similarly, the second Randomized Intervention Treatment of Angina (RITA-2) trial, which compared medical treatment with percutaneous coronary intervention in patients with stable angina, showed that 70% of patients who underwent coronary revascularization used more than one angina medication.[5] Results from the ORBITA study- a randomized, double-blind, controlled study comparing standard medical treatment plus radiotherapy and percutaneous coronary intervention with standard medical treatment plus false procedures—showed no significant differences between the two groups in terms of exercise time, peak oxygen consumption, and control of chest pain.[6] Overall, the available research data show that patients with stable coronary artery disease, including those who have undergone coronary revascularization, require drugs to reduce angina and to reduce symptoms, increase exercise capacity, and improve their quality of life.

Pharmaceutical therapy remains the cornerstone of stable angina treatment. Many Western medicines have been introduced to reduce the symptoms of angina, from classic drugs such as sympathetic beta blockers, calcium channel blockers, and nitrates to drugs like trimetazidine and ranolazine.[2] Similarly, oriental medicines have been applied for the treatment of patients with cardiovascular diseases in general, and coronary diseases in particular, and they have shown positive signs of prophylaxis.[7,8] One example is Tongxinluo, an oriental medicine that has been studied in patients with ischemic heart disease.[9] A meta-analysis of 16 studies with 1,063 patients with general coronary artery disease showed that Tongxinluo administered following placement of a coronary stent reduced the rate of re-stenosis of the stent and reduced the symptoms of chest pain.[10]

A meta-analysis of 18 studies with 1413 patients with unstable angina indicated that Tongxinluo administration helped reduce the risk of myocardial infarction and improved disease symptoms.[11] Several studies have been conducted with small sample sizes, but even the authors of the two meta-analyses stated that the quality of the research designs is still limited, and that higher quality studies are needed that use larger sample sizes.[10,11]

A few studies on patients with stable ischemic heart disease have recorded the clinical effect of Tongxinluo, administered alone or as a complement to routine treatment, on the reduction of symptoms in patients. The general characteristics of these studies still indicate the presence of many confounding factors, including the use of modest sample sizes and a study area limited mainly to China.[12,13] For these reasons, additional studies are needed that have a better design, large sample sizes, multicenter inclusion, and implementation in countries outside of China. Our aim in the present study was therefore to conduct a clinical trial to examine whether Tongxinluo supplementation during the routine treatment of

stable ischemic heart disease would improve angina symptoms and exertion ability in Vietnamese patients.

METHODS

Ethical considerations

The study was conducted with the approval of the Ethics Council in Biomedical Research at Cho Ray Hospital, signed on November 27, 2018. Written consent was provided by all patients to warrantee that they understood the purpose of this study.

Study design

This was an open-label clinical trial with one branch conducted on 300 Vietnamese patients at Cho Ray Hospital between December 2018 and August 2019. Cho Ray Hospital is the largest general hospital in southern Vietnam and takes responsibility for thousands of severe cases from local hospitals daily.

Sampling

The diagnosis of stable angina followed the 2013 European Society of Cardiology (ESC) Guidelines: Patients with an old myocardial infarction or coronary angiography or coronary computed tomography (CT) scan showing at least one primary branch with a degree of stenosis of 50% or more, or patients who had a coronary stent or who had undergone coronary bypass surgery.[2]

Admission criteria: Outpatients, diagnosed with stable angina, who were undergoing regular medical treatment with anti-angina medications according to the ESC Guidelines, patients who agreed to participate in the study and signed a consent form to participate in the study.

Exclusion criteria: Patients with acute coronary syndrome, IV-grade angina according to the Canadian Cardiovascular Society (CCS) criteria, stroke or transient ischemic attack, uncontrolled heart failure, heart valve conditions, arrhythmias, disorders of conduction, uncontrolled hypertension, liver disease with elevated liver enzymes, renal failure with glomerular filtration rate <30 mL/min, anemia with hemoglobin <100 g/L, hemorrhage, women who were pregnant, breast-feeding, or menstruating, patients with exhaustion (BMI<18.5), patients allergic to the components of Tongxinluo, or patients with contraindication for electrocardiograms (ECGs).

Data collection

After each patient was enrolled in the study, the symptoms of angina (including frequency of pain, duration of pain, and severity of pain) were recorded and the patient underwent a clinical examination, basic tests, color Doppler echocardiography, and evaluation of exercise ability by rolling-pad electrocardiogram record exercise time and metabolic equivalent (MET) index with an electrocardiograph.

The patients were provided Tongxinluo at a dose of 6 orally administered tablets twice daily (according to the recommended prescription dose information). The patients were reassessed for symptoms of angina and subclinical side effects of the drug at 2 weeks and 6 weeks after initiation of the drug use. A second ECG was recorded at week 6. A summary of the study process is depicted in **Figure 1.**

Information about the medicine used in this research

The Tongxinluo capsules used in this trial contained Ginseng Radix et Rhizoma (Araliaceae; Chinese ginseng), Paeoniae Radix Rubra (Paeoniaceae; Chinese peony), Semen Ziziphi Spinosae (Rhamnaceae; jujube seed) (fried), Dalbergiae Odoriferae Lignum (Fabaceae; Huanghuali wood), Santali albi lignum (Santalaceae; sandalwood), Olibanum (Burseraceae; Boswellia) (prepared), Hirudo (Haemopidae, leech), Scorpio (Buthidae; Chinese scorpion), Scolopendra (*Scolopendra subspinipes mutilans* L. Koch), Periostracum Cicadae (Cicadidae; cicada), Eupolyphaga Steleophaga (Corydiidae; Woodlouse), and Borneolum (Borneolumsyntheticum). The criteria for the quality of the herbs we used were in compliance with the 2005 Chinese pharmacopoeia.[14] The medications were provided by Shijiazhuang Yiling Pharmaceutical Co., China. This drug has been circulated in Vietnam.

Criteria for subject withdrawal

Patients were withdrawn from the study if they displayed anaphylactic reactions involving drugs, abnormal bleeding; severe abnormal laboratory symptoms, signs, and tests; non-compliance with the treatment; poor tolerance of the drug; worsening chest pain; acute coronary syndrome; and hospitalization for another acute illness.

Research outcomes

The primary outcome was improvement from baseline in the symptoms of angina (including frequency of pain, duration of pain, and severity of pain) and/or increased ability to exercise, determined with a noninvasive probe (ECG using roller mats) as exercise time parameters and METs index six weeks after using the drug.

Statistical analysis

Data were entered and managed using Stata 13.0 software. Continuous variables were presented as mean±standard deviation, nominal variables were presented as percentages. The 6-week post-treatment outcome parameters were compared with the baseline levels measured prior to Tongxinluo administration. The paired t-test was used to compare continuous variables, and the Wilcoxon test was use to compare variables that did not have a normal distribution.

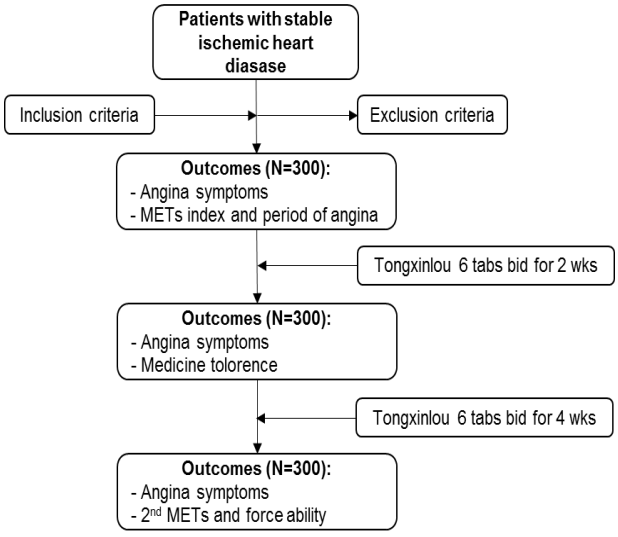

Figure 1. Flow chart for data collection

RESULTS

During this study, all 300 enrolled patients were followed and all completed the study process. The included patients were standardized according to the recommendations of the ESC based on the rate of use of prognostic improvement drugs, such as angiotensin-converting-enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) (99.7%), platelet

aggregation resistance (100%), and statin (100%) (**Table 1**). The proportions of patients with severity of chest pain scores of CCS I, II, III, IV before supplementing with Tongxinluo were 15.0%, 69.7%, 15.3%, and 0%, respectively (**Table 2**). **Table 3** shows the patients' subclinical parameters before and after 6 weeks of treatment.

Side effects reported during the 6 weeks of treatment with Tongxinluo therapy are presented in **Table 4**. Common effects were halitosis, a burning sensation, diarrhea, and headaches. Only one case had low gastrointestinal bleeding, but that was attributed to external hemorrhoids. Other side effects have been reported in previous studies. All side effects were mild and transient during the study or were tolerated. In no case did Tongxinluo need to be discontinued due to side effects.

Table 1. Characteristics of the included patients

Characteristics	N (%)
Age (year), mean±SD	65.2 ± 8.9
Male	133 (44.33)
Body mass index (kg/m^2), mean±SD	22.4 ± 1.4
History of	
Hypertension	300 (100)
Dyslipidemia	300 (100)
Smoking	133 (44.3)
Diabetes	64 (21.3)
Heart failure	49 (16.4)
Coronary revascularization	27 (9.0)
Medication used	
Beta blockers	290 (96.7)
Calcium channel blokers	63 (21.0)
Ivabradine	37 (12.3)
Nitrate	133 (44.3)
Trimetazidine	34 (11.3)
Number of medication used	
Mean±SD	1.86 ± 0.77
Used 1 type of angina medication	99 (33.0)
Used 2 types of angina medication	154 (51.3)
Used 3 types of angina medication	36 (12.0)
Used ≥4 types of angina medication	11 (3.7)

Table 2. Changes in characteristics of chest pain and exertion prior to and after Tongxinluo treatment for catheterization

Variables	Baseline (N = 300)	After 6 weeks (N = 300)	P value*
Frequency of angina (times/week), mean±SD	3.78 ± 0.75	0.69 ± 1.08	<0.001
Period of angina (min/time), mean±SD	3.06 ± 0.71	0.54 ± 0.86	<0.001
Severity of angina (CCS level), mean±SD	2.00 ± 0.03	1.08 ± 0.01	<0.001
ECG time (min), mean±SD	5.46 ± 3.17	6.56 ± 2.90	0.001
METs (watt/kg), median (Q1-Q3)	3.47(3.47 - 4.64)	4.64 (3.47 - 6.30)	<0.001

CCS: Canadian Cardiovascular Society
ECG, Electrocardiography
MET: Metabolic equivalents
*t-test or Wilcoxon test

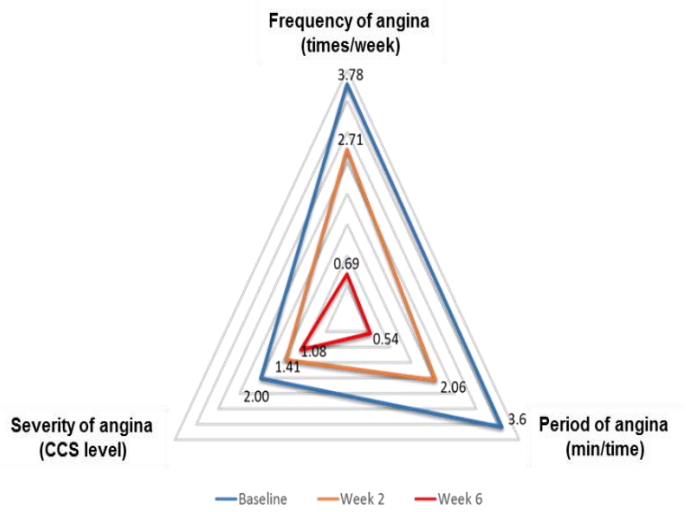

Figure 2. Changes in the properties of angina symptoms at baseline, 2 weeks, and 6 weeks after taking Tongxinluo

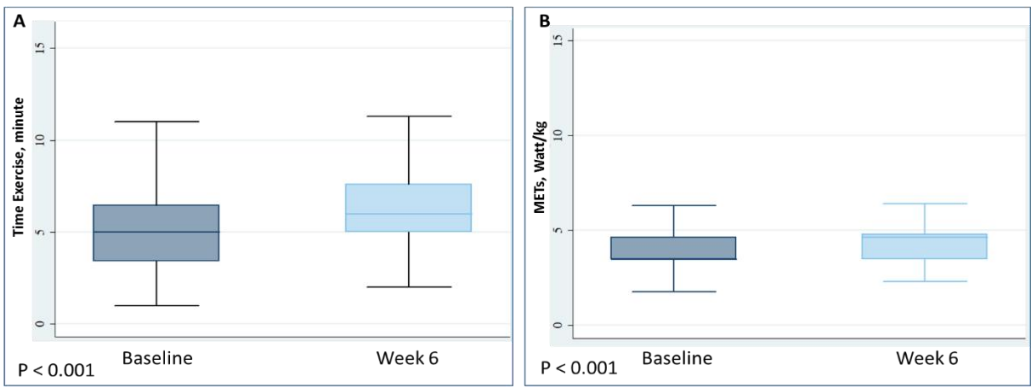

Figure 3. Changes in exercise time on rolling mats and metabolic equivalents (METs) before and after 6 weeks of treatment with Tongxinluo

Table 3. Subclinical parameters before (baseline) and after 6 weeks of treatment with Tongxinluo

Variables	Baseline* (N = 300)	After 6 weeks* (N = 300)	Reference value
Glucose (mg/dL)	101.3 ± 25.2	98.5 ± 25.6	70-110
Cholesterol (mg/dL)	152.4 ± 30.4	141.4 ± 30.5	140-239
Triglyceride (mg/dL)	195.1 ± 76.2	189.1 ± 76.1	35-160
ALT (U/L)	30.7 ± 12.2	31.0 ± 12.2	5-49
AST (U/L)	28.4 ± 7.5	26.3 ± 7.52	9-48
BUN (mg/dL)	18.2 ± 4.6	17.2 ± 4.6	7-20
Creatinin (mg/dL)	1.01 ± 0.21	1.00 ± 0.21	0.7-1.5
RBC (T/L)	4.6 ± 0.3	4.5 ± 0.4	3.8-5.5
WBC (G/L)	8.2 ± 1.6	8.0 ± 1.7	4-11
PLT (G/L)	245 ± 48.6	265.1 ± 48.7	200-400
INR	0.97 ± 0.04	0.96 ± 0.04	1-1.2
aPTT (sec)	29.7 ± 3.1	30.6 ± 3.2	26-37

** Data presented as mean±SD.*

Table 4. Side effects reported for Tongxinluo

Side effects reported for Tongxinluo *	N
Halitosis	8
Burning sensation	5
Diarrhea	3
Headache	2
Dizziness	1
Dysentery[$]	1

*Total number of reported side effects; a patient may have suffered from more than one side effect.
[$] Patient had hemorrhoids.

DISCUSSION

Our study has shown that catheteric drugs help to significantly reduce the incidence of patients' chest pain and to improve the ability to exercise, measured using noninvasive probes (electrocardiograms), in terms of time, exertion, and METs. Previous meta-analyses have indicated a role for catheterization in improving the symptoms of chest pain and the changes in ECG (manifested via ST elevation); this occurred in patients with coronary artery disease with coronary stents and in patients with unstable angina, but Chinese patients showed a decreased tendency for improved cardiovascular outcomes.[10,11] An analysis of 20 studies with a number of patients showed that Tongxinluo is more effective by at least 50% in reducing chest pain when compared with isosorbide dinitrate, and it improves ST segment elevation when ECG is performed on exercise exertion in patients with stable ischemic heart disease.[12]

Our evaluation of the exertion capacity of the patients after the use of Tongxinluo is objective because it is based on ECG exertion with exercise time and METs. The METs index is one of the important parameters used to assess a patient's ability to exercise and is valid for prognosis in patients with ischemic heart disease.[15] Our study showed a statistically significant increase in METs after 6 weeks of Tongxinluo use (**Figure 3**).

The mechanism underlying the potential benefit of cardiac catheterization as a treatment for cardiovascular disease in general, and ischemic heart disease, in particular is still unknown.[7,8] Tongxinluo reduces the symptoms of chest pain through mechanisms that improve endothelial function and microcirculation. A study published in 2018 showed an increase in nitric oxide (NO) levels and a decrease in Endothelin 1 in the Tongxinluo group compared to the control group after 12 weeks of drug use.[16] Yuan et al. showed that Tongxinluo improved apolipoprotein E deficiency in rat myocardial cells and reduced atherogenesis while improving endothelial function.[17] The CAPITAL study-a double-blind, randomized, multicenter trial-demonstrated a role for Tongxinluo in regressing atherosclerotic plaques and improving long-term outcomes for patients.[18] Evidence for the mechanism of action of Tongxinluo based on molecular biology and subclinical indicators indicates that Tongxinluo can reduce ischemia in myocardial cells, thereby leading to clinical improvement of the patient's chest pain symptoms and increased exercise capacity. The results of our study for the Vietnamese population are theoretically consistent and similar to the previously reported results.[12,13]

We also monitored our Vietnamese patients' tolerance to Tongxinluo medication and found no significant or serious side effects (**Table 4**). The side effects observed in our patients have also been noted in previous studies, as well as with other medication prescription.[14] Most of the side effects of Tongxinluo are mild, transient, and tolerable, and in no case did treatment have to be discontinued because of side effects. The dose of Tongxinluo in the study was 6 capsules per day, which is equivalent to the dose administered in previous studies and is in accordance with the prescribed dose of the drug. This was an open-label experimental study, so we were unable to avoid potential interference factors that can occur during open-label testing, such as the placebo effect. Therefore, a need remains for blinded, well-controlled studies that avoid confounding factors.

CONCLUSION

Tongxinluo significantly reduced the symptoms of angina in terms of frequency, duration, and severity. Concomitantly, the ability to exercise, as monitored by electrocardiography, significantly improved after dosing. Tongxinluo was well tolerated by our Vietnamese study population.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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