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Research Article

Symptoms of Intermittent Claudication and Decreased Walking Tolerance in Patients Suffering from Peripheral Arterial Disease can be Improved with a Simple Herbal Supplement

Yan Ping Yen Bryan³, Woo Kam Sang⁴, Kwok Chi Yui Timothy⁵, Chook Ping¹ and Leung Ping Chung^{1,2*}

¹Centre for Clinical Trials on Chinese Medicine, Institute of Chinese Medicine, The Chinese University of Hong Kong, Hong Kong

²State Key Laboratory of Research on Bioactivities and Clinical Applications of Medicinal Plants, The Chinese University of Hong Kong, Hong Kong

³Division of Cardiology, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong

⁴Institute of Future Cities, The Chinese University of Hong Kong, Hong Kong

⁵Division of Geriatrics, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong

ARTICLE INFO

Article history:

Received: 12 February, 2020

Accepted: 2 March, 2020

Published: 22 June, 2020

Keywords:

Peripheral arterial disease

herbal supplement

cardiovascular tonic

ABSTRACT

Introduction: We have developed an innovative herbal formula containing two herbs of popular use for the supplementation of cardiovascular health. Three clinical trials, viz. on patients with coronary arterial obstruction, hypertension, and post-menopausal borderline hyperlipidaemia, have been done, all showing promising results detected in ultrasonography as diminished intima media thickness (IMT), a surrogate marker recommended for clinical trials related to cardiovascular health. 49+49 patients with known peripheral arterial disease (PAD) were treated with twin formula or placebo group for 24 weeks. Assessment using ultrasonography showed thinning down of the carotid intima (2.67%) only in the treatment group. Maximal walking distance also increased by 21.8% in the treatment group compared with 7.2% in the placebo group ($p=0.499$).

Discussion: The positive results in the PAD study as well as in the other studies done previously demonstrated the effectiveness of the twin formula in the maintenance of cardiovascular health. It is safe and offers direct protection of the internal environment of the artery while at the same time carries the multiple roles of anti-inflammation, anti-oxygenation and anti-fibrosis, as were shown in in vitro and animal bioactivity studies.

Conclusion and Outlook: The twin formula offers a good example of evidence-based medicinal supplements with specific functions. Its developmental process also offers a more comprehensive way to test traditional wisdom and practice through pragmatic clinical trials in the attempt to properly introduce it to modern health care practice.

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Introduction

In 2011, we gave a report on the cardiovascular state of patients with known coronary obstructions receiving a simple herbal supplement with the aim of improving the arterial patency [1]. The study patients had completed their standard treatment. At least 2 of their coronary arteries were obstructed, but they were not suffering from severe clinical symptoms, which, if occurred, would be treated by the cardiologist.

Ultrasonic assessment of the intima media thickness (IMT) of the carotid artery and flow-mediated endothelium-dependent dilation (FMD) were used as surrogate markers [2, 3]. The effectiveness of using the herbal supplement had been remarkable. After six months of treatment, IMT decreased 0.96 ± 0.32 mm, while FMD improved $5.9\% \pm 1\%$ [1].

The herbal supplement consisted of two herbs of popular use, viz. *Salviae miltiorrhizae radix* and *Puerariae lobatae radix*. Historically, *Salviae* had been selected as a component of many herbal formulae

*Correspondence to: Leung Ping Chung, 5/F, School of Public Health Building, Prince of Wales Hospital, Shatin, Hong Kong; E-mail: pingcleung@cuhk.edu.hk

related to cardiac symptoms, while *Puerariae* was a common household cooking material used this time as an innovative partner in the twin formula [4]. Whether the two herbs combined would have special cardiovascular supportive effects needs to be proven with basic bioscience experiments. Indeed, subsequently, series of platform studies have been completed to confirm many unique bioactivities of the twin formula: including its anti-inflammatory and anti-oxidative effects, vascular protection effects and vasculogenic potentials [5-11]. Subsequently, the twin formula was tested in two more clinical applications.

To evaluate the potential of the twin formula for primary atherosclerosis prevention in high-risk hypertensive patients, 90 patients (74.4% male) with hypertension associated with left ventricular hypertrophy (63.3%), diabetes mellitus (62.5%), and renal insufficiency (30%) were randomized to receive the twin formula or identical placebo capsules in a double-blind and parallel fashion for 12 months, on top of their anti-hypertensive treatments. Results showed that FMD and IMT improved significantly after the twin formula but not after the placebo treatment [12].

Later, a population-based sample of 165 postmenopausal women who experienced menopause for more than 12 months was recruited for the study of the preventive effects of the twin formula. These volunteers had border-line hyperlipidemia. Results showed that the carotid IMT decreased 1.52% from the baseline in the twin formula group ($P < 0.004$), but the decrease was only 1.13% for the placebo treatment group after a 12-month treatment [13].

The Present Study

The aging arterial system affects all vessels at various sites: from coronary to smaller vessels which affect blood pressure. Medium-sized arteries occur in the limbs, and in the lower limbs, if their patency is affected and blood flow becomes deficient, symptoms of “peripheral arterial disease” (PAD) become manifest. The prominent symptoms included intermittent claudications and diminished walking distances (limited by the painful symptoms and calf spasm). The peripheral arterial disease could be related to hypertension, and diabetes mellitus, making the situation more worrying. Progressive deteriorations of the arterial state lead to progressive distal ischaemia which might result in gangrene of the toes and possibly ending in amputations [14]. In view of the happy experience using the twin-herb formula in three clinical trials, the cardiologist designed a suitable protocol to make use of the twin formula to alleviate the symptoms of intermittent claudications in well-established cases of PAD.

Methods

I Design of Clinical Trial

A prospective, double-blind, placebo-controlled clinical trial lasting 24 weeks for 100 patients with known PAD was organized. The inclusion criteria were age above 40, suffering from intermittent claudications ranging from grade 1 to 3, and post-exercise ankle-brachial index < 0.90 . Selected patients did not experience any serious lower limb ischaemia, neither did they receive any vascular reconstructions.

II Treatment

98 patients were successfully recruited. 2 groups of 49 each were randomly assigned as treatment or placebo group. Production of the innovative twin formula was accomplished using best quality herbs grown in the acclaimed areas in China and subsequently made into 500 mg capsules in a laboratory of GMP standard. Placebo capsules were produced by the same laboratory strictly following the guidelines. Patients were given 3 capsules of the twin formula or placebo two times a day for a period of 24 weeks.

III Assessment of Efficacy

Apart from keeping a detailed pre- and post-treatment clinical record of standard symptoms and signs for PAD, two specific parameters were crucial for the assessment of efficacy. They were maximal walking distance (MWD) detected from treadmill walking (until claudication was experienced) and IMT of the carotid artery, a universally accepted surrogate marker for the arterial state. The intra-arterial state was assessed by measuring IMT.

IV Statistical Analysis

100 patients were recommended as the total number of clients basing on the assumption that improvement might reach an increased walking distance of 20 meters, SD 30, then reaching a 90% successful study. SPSS software was used to deal with the last observation carried forward (LOCF) problem. Paired t-tests would be suitable to compare the treatment and placebo groups, and $P < 0.05$ would be considered statistically acceptable.

Results

I Baseline Comparison between the Two Groups Confirmed They were of Comparable Nature

Table 1: Some Basic Information Between the Two Groups.

Patients	Twin Formula Group	Control Group	P Value
Gender (M)	34 (69.4)	39 (79.6)	0.247
Smoker	21 (42.9)	22 (44.9)	0.839
DM	26 (53.0)	28 (57.1)	0.685

II MWD of the Two Groups Before and After Study

Table 2: After 24-week treatment, the twin formula group MWD increased 21.8% compared with only 7.2% in the placebo group ($P=0.499$).

Patients	Twin Formula Group	Control Group	P Value
Age	66.2±9.4	68.5±7.5	0.187
Index (kg/m ²)	24.8±4.2	24.2±3.5	0.420
Systolic BP	144.7±16.9	150.5±21.5	0.142
Diastolic BP	71.9±10.4	73.6±11.9	0.460
IMT (mm)	1.159±0.624	1.083±0.343	0.456

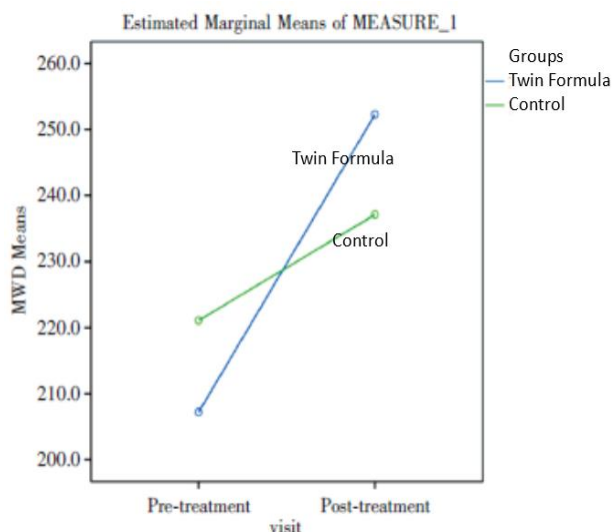


Figure 1: Pre- and Post-treatment changes of MWD.

III Ultrasonic Evaluation of Carotid Artery IMT Indicated a Decrease of 2.67% in the Twin Formula Groups Compared with Nearly No Change in the Control Group

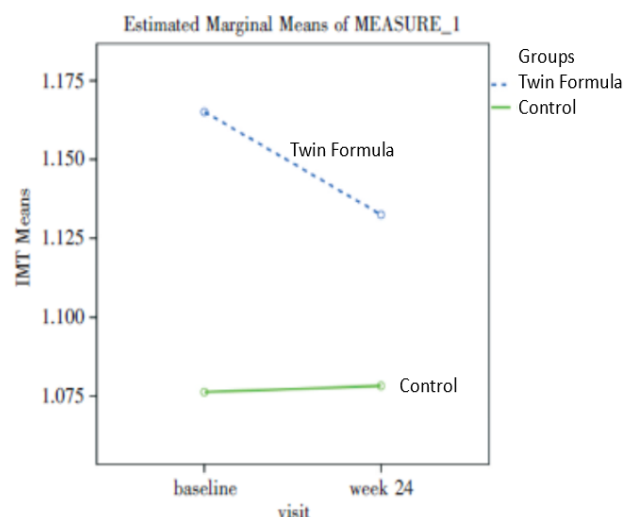


Figure 2: Pre- and Post-treatment changes of IMT.

Discussion

As the human survival rate improves with advancing age, the incidence of PAD increases [14]. The progressive symptoms of intermittent claudication severely limit the activities of daily living of the PAD patients. While interventions to maintain the blood flow in the lower limbs of PAD patients are available and could be effective, many other cases might not be able to get the maximal benefits with the interventional procedures like stenting or bypass operations, since the obstruction could be extensive, multiple, or too distal [15]. Non-surgical means, if proven effective, will be a great help to such patients. As a matter of fact, PAD patients are often victims of multiple pathologies, showing a much higher incidence of coronary and cerebral involvement making active intervention even more difficult [16].

The twin formula consisting of herbs of common household use could be safely applied as an evidence-based specific supplement to improve

vascular flow. As a matter of fact, narrowing down of the arterial lumen involves multiple pathological interactions, which include inflammation, smooth muscle spasm, platelet accumulations and intimal cellular metabolic malfunctions, etc. Mechanical correction applied as the major means of correction might work well in the short term only since the multiple pathological interactions still remain [16, 17]. In the situation of complete arterial block, the distal blood supply actually relies on multiple tributaries and collaterals. A sudden open up of the major block, e.g., in a stenting procedure, might even initiate a very much dreaded “no-flow phenomenon”, leading to sudden complete distal ischaemia [18].

The twin formula has been studied extensively in the past 20 years and found to be able to effectively control inflammation, relax vascular smooth muscles and even help to lower circulating blood cholesterol. Its multiple dimensions of cardio-tonic effects would be beneficial to many different areas of arterial insufficiencies affecting a divergent variety of physiological activities: from coronary and cerebral function to more regional areas like PAD.

Conclusion and Outlook

Plant-based medicine has made tremendous historical contributions among ethnic groups, towards their general and special needs. Traditional Chinese medicine can be considered a huge system of therapy that particularly emphasizes on herbal treatment and supplements. Today we consider such practice as “Herbal Pharma therapy and Food: as complex interventions to support conventional treatment [19]. Most claims on food supplements are not based on strict pharmacological approaches but on epidemiological, histological observations, or in-vitro platform studies [20]. In spite of the lack of perfect justification, herbal supplements still enjoy advancing popularity [21]. One reason is related to the overutilization of costly treatment that might not be able to produce the expected quality of care. If supportive therapy like plant-based supplements can be proven to give effective specific supportive roles in standard treatment, it is going to occupy a unique position in the overall healthcare system, which currently appears to be underutilizing effective treatment [22].

In the past 18 years, we have been working on a research methodology that could possibly bring plant-based medicine closer to the effective treatment need. We identify areas of current need, which are often related to aging (like our presentation on cardiovascular health); then, we study classic records of herbal treatment to create an innovative formula (like the twin formula). Such a formula is strongly related to ethnopharmacology since it carries a strong traditional origin, and the herbs selected need to be assured of quality [20]. The formula is then put onto bioactivity platforms to investigate its effectiveness like anti-inflammation, anti-oxidation, and in the case of PAD, specific properties related to cardiac health like blood lipids, vascular intima and flexibilities. When such in-vitro efficacies are proven, the formula could be put to proper clinical trials. The component herbs are well known and popular, hence, toxicity is not of major concern. The clinical trial protocol resembles one of the standard phase 2 to 3 level trials and the outcome of which gives sufficient evidence of effectiveness [11].

This paper describes the clinical results of the twin formula used to improve the symptoms of PAD. It serves as an example of how an evidence-based specific supplement could be developed. It is our belief

that plant medicine offers not only phytochemical molecules for drug discovery but could be developed into effective treatment options in support of standard conventional therapy [23-25].

Ethical Approval

Proper approval from the regional ethics committee was obtained (2012.561-T).

Consent

All patients signed their consent forms.

Acknowledgements

This study was supported by Grants on State Key Laboratory of Research on Bioactivities and Clinical Applications of Medicinal Plants (The Chinese University of Hong Kong) from HKSAR and The Chinese University of Hong Kong.

Author Contributions

Leung Ping Chung: Responsible for the preparation of the manuscript. Yan Ping Yen Bryan: Principle Investigator of the PAD trial. Woo Kam Sang: Principle Investigator of the Coronary trial. Kwok Chi Yui Timothy: Principle Investigator of the Menopausal Trial. Chook Ping: Took care of all the sonographic assessments.

Abbreviations

IMT: Intima Media Thickness

PAD: Peripheral Arterial Disease

FMD: Flow-mediated endothelium-dependent dilation

GMP: Good Manufacturing Practice

MWD: Maximal Walking Distance

LOCF: Last Observation Carried Forward

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