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Additive Effect of Moxibustion Therapy and Treadmill Exercise as a Treatment for Intermittent Claudication Associated with Peripheral Arterial Disease

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Abstract

Objective: To determine the effect of moxibustion combined treadmill exercise on subjects with peripheral arterial disease (PAD).

Methods: 80 PAD patients were randomly assigned into a control group (CG, n=20), a moxibustion therapy group (MG, n=20), a treadmill exercise group (TG, n= 0) and a moxibustion therapy combined with treadmill exercise group (MTG, n=20) with the treatments of 18 weeks. Outcome measurements were lower limbs' transcutaneous oxygen tension ($TcPO_2$), treadmill-walking test to determine when claudication pain begins and how long it takes to reach the maximum claudication pain, 6-minute walking test (6MWT) and walking impairment questionnaire (WIQ).

Results: MG, TG and MTG treatment groups showed a significantly better curative effect ($p<0.05$) in all of the outcome measurements. Compared to MG, the TG and MTG showed significantly more improvement in the treadmill exercise test as well as in the 6MWT and WIQ ($p<0.05$); compared to TG, MTG was better in treadmill walking time to reach maximum claudication pain, 6MWT and the stair-climbing capability in WIQ ($p<0.05$).

Conclusion: Moxibustion therapy in combination with treadmill exercise can improve the lower limber microcirculation, relieve symptoms of intermittent claudication, and improve quality of life of PAD patients. Moxibustion combined with treadmill exercise shows further improvement in low limber exercise capacity.

Keywords: Moxibustion; Treadmill exercise; Peripheral artery disease; Exercise capacity

Introduction

Peripheral arterial disease (PAD), defined as atherosclerosis of the peripheral vessels, is becoming a major global health issue. Clinically, PAD can manifest as an intermittent claudication or even severe limb ischemia, resulting in a loss of mobility due to pain, decreased quality of life, and an increased risk of more severe cardiovascular diseases [1]. Epidemiological data suggests that PAD affects about 20% of people over the age of 60 and that rate is even higher in China [2]. Although PAD is rarely the direct cause of death, it is closely associated with an increased risk of cardiovascular diseases such as heart attack and stroke. Currently, PAD receives little attention in China with limited treatment approaches such as antiplatelet and antithrombotic drugs, and surgery for severe cases [3].

In western countries, supervised treadmill exercise has been proven to improve patients' exercise capacity significantly and is a major treatment of PAD [4]. Studies have shown that efficacious treatments for PAD, such as treadmill exercise, often result in improved function of vascular endothelial blood flow, improvement of mitochondrial function, and increased intensity of the capillary vessels to improve blood supply from the peripheral arteries [5].

Traditional Chinese medicine identifies PAD as associated with the traditional Chinese theory of "pain due to obstruction," or Bi syndrome. In China, moxibustion has been used as an effective method to alleviate the symptoms of joint pain by stimulating blood flow by warming meridian points and regions on the body using burning moxa. Moxibustion in combination with drug treatment is a common therapy to treat the symptoms of PAD in China. However, the efficacy of the combined therapies has never been systematically investigated.

Current research on PAD treatment is aimed at not only treating the painful symptoms of PAD, but also reducing or eliminating the causes of PAD such as the fatty blockages in blood vessels due to obesity, smoking, and other unhealthy lifestyles. In line with this, a combination therapy of treadmill exercise and moxibustion may provide the most significant relief of symptoms of PAD and, more importantly, increase peripheral vascular health.

In this study, we use moxibutstion therapy and treadmill exercise to reduce the intermittent claudication caused by PAD. Reduction in the pain associated with PAD without the use of pharmaceutical therapies will provide a better quality of life.

Methods

Subjects

This study was approved by the ethics committee of Jiangsu Provincial Hospital. Study purpose, nature and its potential risks of this trial were fully explained to the patients, and all subjects provided their written, informed consent prior to participation. Subjects were free to withdraw at any time when they or their custodian requested discharge from the study.

In total, 80 patients with mild or moderate PAD were recruited from the outpatient department of cardiology at Jiangsu Provincial Hospital from March 2013 to June 2014. The PAD Guide, revised by ACC/AHA in 2011, and the PAD Guide in China were used to determine PAD diagnostic criteria. The Ankle-Brachial Index (ABI) was used as the diagnostic reference of PAD to evaluate the peripheral circulation status and severity of disease with normal levels defined as 0.91~1.30, mild PAD as 0.71~0.90, moderate PAD as 0.41~0.70, and severe PAD as 0.00~0.40[6]. The inclusion criteria for this study were mild and moderate PAD and being 45-70 years old. Any patients who suffered from unstable acute coronary artery syndrome after treatment, uncontrolled sever arrhythmia, hypertension, and diabetes mellitus were excluded from this study. Additionally, patients who were unable to cooperate with physical exercise due to bone, joint, muscle, nervous disease, deep vein thrombosis within 3~6 months of the beginning of the study, or underwent recent surgery for lower limbs artery reconstruction were excluded from the study.

Patients were randomly assigned to one of four groups, control group (CG), treadmill exercise group (TG), moxibustion group (MG), and moxibusion plus treadmill exercise group (MTG). All patients were provided with health education that focused on the importance of smoking cessation, and a healthy diet was provided to all subjects. Basic medications that control plasma glucose, blood pressure, stabilize blood lipid content, and inhibit platelet aggregation were administered as prescribed by each patient's primary care physician. PAD patients with hypertension were under diuretics, ACEI, or β-blockers and other types of antihypertensive medication; Patients with high blood cholesterol were under statins treatment to reduce blood fat; Patients with high blood sugar were either using oral medication or insulin to control their blood sugar. All patients were taking antiplatelet drugs such as aspirin and clopidogrel.

For the treadmill exercise in TG and MTG groups, patients performed a 5-minute warm up exercise followed by ambulation training on a SportsArt treadmill (T652M, United States). Each individual patient's workload was set at onset of mild ischemic pain symptoms after a 3~5 minutes of training. Patients continued with the same workload until moderate ischemic pain symptoms appeared, at which point they took a short break by standing or sitting down until the symptoms of moderate ischemic pain disappeared or subsided. Once the pain subsided, patients repeated the exercise-rest-exercise session with the same or a progressively increased workload. Treadmill treatment occurred over the course of 50 minutes per session including warm-up and rest at a frequency of 5 times per week over a period of 18 weeks.

During the treadmill training, heart rate and blood pressure were monitored closely. When symptoms such as progressive chest pain, dizziness, ataxia, general fatigue, and shortness of breath appeared, patients were instructed to cease the session or reduce the workload immediately.

For the MG and MTG groups, warming moxibustion was performed on acupuncture points "Zusanli" or st36 and "Sanyinjiao" or sp6 on the lower limbs. Patients were placed in a supine position and with the skin of their lower limbs exposed. A moxa-stick was lit and positioned between 3 to 5 cm away from patient's skin depending on the patient's skin sensitivity to heat. The distance was considered ideal when subjects felt heat without feeling scorching heat. Moxibustion was performed five times per week, and was applied 15 minutes per acupoint over the period of 18 weeks.

Evaluation methods

To evaluate the severity of PAD a transcutaneous oxygen tension ($TcPO_2$) test was performed, analysing the pressure of oxygen tension at the level of the skin. Patients were placed in a supine position and, after 20 minutes of rest, probes of a radiometer (TCM400, Radiometer Medical A/S Company, Denmark) were placed at the back of the triceps surae, and the temperature of the probe was set to 45 Celsius. Data was recorded and analysed.

The severity of intermittent claudication was assessed two ways: the American GE ECG treadmill exercise test and a 6-minute walking test. The treadmill exercise test involved patients walking on a treadmill beginning at 2 mph with a 0% slope. The slope would increase every 2 minutes at a 2% slow increase. Patients continued at this rate until claudication pain was present. The severity of claudication pain was categorized into five grades, with level 0 for no pain, 1 for onset of induced pain, 2 for mild pain, 3 for moderate pain, and 4 for severe pain. Time was recorded when the corresponding pains of levels 1 and 4 appeared. At the same time, electrocardiogram and blood pressure were monitored. For the 6 Minute Walking Test (6MWT), patients were instructed to walk back and forth along a 30-meter straight line marked on the floor for 6 minutes. While walking, patients were instructed to adjust their speed according to their own conditions, and to stop and take a rest if they experienced uncomfortable symptoms, such as moderate to severe pain in lower limbs. They were then instructed to resume walking when they were able to continue. The distance that each subject walked was recorded.

To determine whether there was a change in perceived mobility of the patients based on treatment, patients were asked to answer a Walking Impairment Questionnaire (WIQ) [1] consisting of 14 questions about walking distance, walking speed, and ability to walk on the stairs. The 14 items were scored on a Likert 4-count with "4" being "no difficulty", and "0" being "unable to complete". The dimension score is equal to respective score of every item × (distance +speed+step number)/highest score of the dimension. Scores in each section range from 0 to 1 with lower scores indicating the greatest adverse impact on patients' walking impairment. Meanwhile, the average score of the three parts was regarded as the total score of WIQ scale score.

Statistical analysis

Statistical software SPSS17.0 was employed to analyse data. A non-parametric test was performed to compare between groups and a Student's t-Test was performed to compare the measurement data within a group. One-way ANOVA of randomized design data was performed to examine effect of time and intervention on all outcome measurements. SNK-q test was employed when main effects were detected. Significance was set at $p<0.05$.

Characteristics	CG	MG	TG	MTG
Gender (male/female)	12/7	13/7	12/7	12/8
Smoker	8	9	10	9
Diabetes Mellitus	9	10	11	10
Hypertension	8	8	9	10
Mild PAD	10	10	11	9
Moderate PAD	9	10	9	11
Age (y)	58.43 ± 4.96	60.52 ± 5.30	57.20 ± 6.21	61.36 ± 7.25
Course of disease (months)	75.00 ± 32.00	80.00 ± 46.00	78.00 ± 48.00	84.00 ± 42.00
ABI	0.63 ± 0.21	0.62 ± 0.27	0.64 ± 0.29	0.61 ± 0.24

Table 1: Comparison of the general information of all subjects among four groups (x ± s).

Results

There was no statistical significance among subjects in the four treatment groups in terms of gender, age, the associated disease risk factor, and course of disease (Table 1). One patient from the CG group and one patient from TG group withdrew due to unbearable pain during the exercise. No significant difference in $TcPO_2$ baselines (Table 2) was observed between groups before treatment. After 18 weeks of treatment, $TcPO_2$ baseline for the MG, TG and TMG groups all improved significantly over the control group. There was no difference between the MG and TG groups; however the MTG was significantly improved over MG or TG alone.

On the treadmill exercise test (Table 3), the time to onset of claudication pain was the same for all four groups at the beginning of the treatment. After the 18-week intervention, the time to onset of claudication pain and severe claudication pain were significantly delayed in TG, MG and MTG groups when compared to the CG, with the TG and MTG groups outperforming the MG group. The patients in the MTG intervention group performed the best, with a significantly delayed time of onset of claudication pain and severe claudication pain, suggesting moxibusion and treadmill exercise have an additive effect at slowing the onset of intermittent claudication pain.

Group	After	Before
CG (n=19)	61.38 ± 9.02	62.05 ± 9.12
MG (n=20)	61.67 ± 8.62	67.57 ± 8.20[ab]
TG (n=19)	62.15 ± 8.36	68.32 ± 7.87[ab]
MTG (n=20)	60.95 ± 7.98	71.62 ± 7.17[abcd]

Table 2: $TcPO_2$ baseline (in mmHg) comparison before and after treatment (x ± s). [a]Pair comparison before and after treatment, $p<0.05$; [b]Group comparison with CG, $p<0.05$; [c]Group comparison with MG, $p<0.05$; [d]Group comparison with TG, $p<0.05$.

Groups	Time to onset of claudication pain		Time to severe claudication pain	
	Before treatment	After treatment	Before treatment	After treatment
CG (n=19)	3.9 ± 1.6	4.2 ± 2.3	7.2 ± 2.2	7.6 ± 2.8
MG (n=20)	4.0 ± 1.8	5.9 ± 2.4[ab]	7.4 ± 2.5	8.7 ± 3.0[ab]
TG (n=19)	4.1 ± 2.0	6.7 ± 2.9[abc]	7.3 ± 2.8	10.6 ± 3.7[abc]
MTG (n=20)	4.1 ± 1.9	7.1 ± 2.8[abc]	7.1 ± 2.6	12.7 ± 4.0[abcd]

Table 3: Comparison of the treadmill exercise test results before and after treatment (x ± s, min). [a]Compared with pre-therapy, $p<0.05$; [b]Compared with CG, $p<0.05$; [c]Compared with MG, $p<0.05$; [d]Compared with TG, $p<0.05$.

For the 6MWT (Table 4), all four groups performed similarly, walking approximately 220 meters in 6 minutes. After the 18-week treatment, the treatment groups walked farther than the control group. Compared to MG group, the distance of 6MWT increased significantly in both TG and MTG groups. Although the TG and MTG groups outperformed the MG group, there is slight but not significant increase in MTG compared with TG, which indicates that training exercise is necessary to improve patients' mobility, and that the effect of moxibustion and training could be additive.

Table 5 shows the WIQ scores assessing the quality of life of patients of all groups. All four groups scored similarly on walking speed, walking distance, and ability to climb stairs before the treatment. After the treatments, patients in the TG, MG, and MTG groups noted that their walking speed, walking distance and ability of

climbing stairs improved over their baselines and the CG group. Compared to MG group, further improvement on WIQ evaluation was seen in the TG and MTG groups. Although there was no difference in WIQ outcomes between the TG and MTG groups MTG group did perform slightly better than the TG group (for example, the ability of climbing stairs), further suggesting an additive effect of treadmill exercise and moxibustion therapy on the improvement in the quality of life of the patients.

Groups	Before	After
CG (n=19)	217.56 ± 38.25	220.75 ± 41.29
MG (n=20)	220.34 ± 37.62	248.40 ± 48.93[ab]
TG (n=19)	218.70 ± 36.82	267.84 ± 52.64[abc]
MTG (n=20)	219.85 ± 39.02	271.37 ± 54.59[abc]

Table 4: Comparison of the distance of 6MWT before and after treatment (x ± s, min). [a]Compared with pre-therapy, p<0.05; [b]Compared with CG, p<0.05; [c]Compared with MG, p<0.05; [d]Compared with TG, p<0.05.

Groups	Walking speed%		Walking distance %		Ability of climbing stairs %	
	Before	**After**	**Before**	**After**	**Before**	**After**
CG (n=19)	58.62 ± 13.17	60.23 ± 14.35	58.31 ± 13.41	61.21 ± 14.28	78.57 ± 21.37	77.54 ± 19.87
MG (n=20)	57.97 ± 13.57	63.53 ± 17.84[ab]	57.94 ± 13.89	62.40 ± 15.12[ab]	76.43 ± 19.25	80.93 ± 20.67[ab]
TG (n=19)	56.68 ± 12.95	68.47 ± 16.31[abc]	57.56 ± 12.83	67.24 ± 15.34[abc]	77.45 ± 20.03	86.54 ± 21.33[abc]
MTG (n=20)	59.21 ± 13.25	70.29 ± 17.34[abc]	59.24 ± 13.41	68.35 ± 15.98[abc]	77.12 ± 19.82	90.41 ± 20.65[abcd]

Table 5: Comparison of WIQ assessments before and after treatment (x ± s). [a]Compared with pre-therapy, p<0.05; [b]Compared with CG, p<0.05; [c]Compared with MG, p<0.05; [d]Compared with TG, p<0.05.

Discussion

PAD belongs in the Bi syndrome, or "pain due to obstruction", theory in traditional Chinese medicine (TCM). This theory is very similar to the nosogenesis theory in modern medicine. In TCM, moxibustion aims at "warming vessels to lead to resolved obstruction" and "regulating blood flow in vessels." In other words, the warm stimulation promotes the smooth flow of blood in the vessels [7]. Causes of PAD lie in vascular artery stenosis derived from atherosclerosis, which limits the supply of oxygen to the peripheral limbs and thus intermittent claudication appears [8]. Therefore, the mechanism of moxibustion in treating PAD may lie in the improvement of correlative peripheral microcirculation. In support of this theory, infrared thermal imaging and laser Doppler perfusion imaging were used by Huimin Ma [9] to explore the change of temperature and microcirculation perfusion on certain acupoints such as 'Fenglong' or s40, 'Xiajuxu' or s39 and the high temperature zone of skin after electric acupuncture and moxibustion. An increase in blood flow was found on three observed acupoints during manipulation and, for some, the increase in temperature persisted after moxibustion therapy [10]. Furthermore, other studies indicated that moxibustion has a significant treatment effect on key risk factors of PAD such as hypertension [11], high blood lipid [12], and high blood glucose [13]; and it is also of significance in controlling related risk factors. In addition, studies on a rat model of chronic hyperlipidemia found that mild moxibustion can promote the activity of SOD, GSH-px, CAT, and MDA as well as a decrease in serum IL-6, serum IL-8 and TNF-α. Oxidative stress and inflammatory reaction are also effectively inhibited during mild moxibustion with the regulation of blood lipid levels [14]. This is important to control related risk factors in PAD subjects and slowing down the process of atherosclerosis.

Importantly, our study indicated PAD patients who underwent any form of treatment, particularly combination therapy, had a significantly elevated $TcPO_2$ baseline. This is an indication of improvement in the condition of hypoxia of the lower limbs. Our moxibution treatment with treadmill exercise also promoted an increase in walking distance, walking speed, and an ability to walk on stairs. Significantly, prolonged time to the onset of claudication pain in PAD patients indicates improvement in exercise capacity of lower limbs. Our studies are consistent with previous studies, which found that an ambulation treatment twice a week for 6 weeks leads to improvement in walking distance, walking speed and walking duration by 148%, 34% and 94% respectively [8,15].

PAD associated intermittent claudication is caused by a significant reduction in the amount of oxygen reaching the lower limbs due to blockages. Although moxibustion therapy can improve the amount of oxygen reaching the tissues in the lower limbs, it was not as effective as treadmill exercise. Furthermore, moxibustion treatment in combination with treadmill exercise for PAD subjects demonstrated an improvement in the $TcPO_2$ baseline. This suggests that moxibusion therapy in combination with treadmill exercise may be improving blood flow to the affected areas. This is reasonable based on previous studies on moxibusion therapy [10]. It is also possible that these therapies are also aiding in re-vascularization in the tissues of the affected limbs, however more study on this is needed. In addition, all of the recruited PAD patients are under medication as indicated in the method part. Although, these medications are important to reduce the risk factors for PAD, there are no interactions with exercise and moxibustion therapy. The medications are applied to slow down the PAD progression, ameliorate long-term prognosis. However their effects on improving patient transcutaneous oxygen pressure, exercise capacity and quality of life are very limited.

Future studies should examine effect of pain relief and fatigue reduction in PAD patients after receiving moxibustion combined with treadmill exercise. Additionally, it is worth investigating whether moxibustion can be used as a pre-treadmill exercise "warm up". Further studies would benefit from a larger sample size. In addition, it will be important to examine the long term effect and underlying molecular mechanism related to improvement of PAD due to moxibustion and treadmill exercise therapy.

Conclusions

Overall, we showed that a combination of traditional Chinese medicine and western therapy is most effective at reducing the painful symptoms of PAD. Moxibustion and treadmill exercise effectively relieved symptoms of intermittent claudication, improved quality of life in PAD patients as indicated in the WIQ assessments and shown in the increased walking distance of patients in the 6MWT. Furthermore,

moxibustion and treadmill exercise can improve exercise capacity of PAD subjects. In addition to an improved quality of life, this study indicates that further studies should focus on the potential for the combination therapy of moxibustion and treadmill exercise to decrease the necessity for excess medications such as antiplatelet, antithrombotic, and pain killers as well as reduce the need for surgery.

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