

Effect of Tongxinluo Capsule on Patients with Syndrome X and Affective Disorder

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Abstract

Background: To explore the therapeutic effect of Tongxinluo capsule (Tongxinluo) on patients with Syndrome X and Affective Disorder. **Methods:** Fifty-six patients with Syndrome X and Affective Disorder were randomly divided into a Tongxinluo capsule group and a placebo control group. The duration of treatment was 12 weeks. A 6-minute walking test, exercise load electrocardiogram and clinical symptom assessment were performed before and after treatment. After 12 weeks of treatment, the scores of the Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS) were repeated. The levels of serum endothelin-1 (ET-1) and nitric oxide (NO) were measured before and after treatment. **Results:** Compared with the placebo control group, the Tongxinluo group SAS and SDS scores were lower than those before treatment (all $P < 0.01$), and the 6-minute walking distance increased significantly ($P < 0.01$). Clinical symptoms were significantly improved. The exercise test results suggested that, while improved, there was no significant difference ($P > 0.05$) when compared to before treatment. In the Tongxinluo treatment group, the levels of plasma endothelin-1 decreased significantly ($P < 0.01$) and nitric oxide levels were significantly increased ($P < 0.01$), with a significant difference when compared to the control group ($P < 0.01$). **Conclusions:** The Tongxinluo capsule can improve the Affective Disorder of Syndrome X, reduce the degree of anxiety and depression, increase exercise tolerance, reduce clinical symptoms, and improve vascular endothelial function.

Keywords

Syndrome X, Affective Disorder, 6-Minute Walking Test

1. Introduction

Cardiac Syndrome X refers to angina pectoris with chest tightness and chest

pain. It is accompanied by a group of syndromes with a positive electrocardiogram, a positive exercise load electrocardiogram and a normal coronary angiography, which excludes coronary artery spasm. These patients account for 10% - 15% of the total number of patients with angina pectoris. Syndrome X is also known as microvascular angina, and its pathogenesis may be due to the abnormal structure and function of microvessels with a coronary artery less than 300 microns [1] [2]. When found during the clinical treatment of the disease, the condition is hardly a threat. However, some patients are often in a state of anxiety and depression, affecting their daily work and life. It is more likely because women make up a large proportion of patients, not because of doctor's insufficient explanation. The quality of life of family members of patients is affected to different degrees. The study found that patients with Syndrome X complicated by Affective Disorder are in high proportion. Clinical research found that the disease was not a threat to patients' lives, but some patients were often in a state of anxiety and depression, which affected their daily work and life. The quality of life of patients and their families is affected to varying degrees. This may be because female patients are more common and may be related to doctors' understatement of the disease. This study found that the proportion of patients with Syndrome X combined with Affective Disorder is relatively high, similar to those reported by Asbury and Vermeltfoort [3] [4]. Non-interventional therapy is usually used in Syndrome X. The traditional drugs include nitrates, beta receptor blockers and calcium channel blockers. Through the progress of clinical treatment, it was found that nitrates could reduce chest pain but had no significant effect on increasing activity tolerance. Beta receptor blockers can partially reduce the onset of chest pain, but there is no increase in activity tolerance, and it has a risk of aggravating Affective Disorder [5]. The Tongxinluo capsule is a compound preparation of traditional Chinese medicine. Clinical and experimental results showed that the Tongxinluo capsule could improve the symptoms of dizziness in patients with cerebral infarction and relieve chest pain symptoms in patients with coronary heart disease, and according to previous studies, improve endothelial function, reduce the clinical symptoms of patients, and increase activity tolerance [6]. The effects of the Tongxinluo capsule on the treatment of Syndrome X have not been reported in patients with Affective Disorder before. Its role is reported as follows.

2. Data and Methods

2.1. Patient Recruitment

From June 2015 to September 2017, 56 patients with symptoms of angina pectoris were hospitalized in the Department of Cardiology at the First People's Hospital of Kunshan City under the evaluation of the self-rating anxiety scale and self-rating depression scales. Inclusion criteria: all patients had a positive exercise test and no stenosis found in coronary ateriography. Scores were higher than 50 in the SAS and SDS tests, and all patients signed their informed consent.

Exclusion criteria: patients above age 70, with severe liver or renal insufficiency, or tumour and haematological diseases were excluded. Among the patients, there were 16 males and 40 females, aged from 46 - 70 years, with an average age of 56 ± 16 (Table 1, Table 2).

2.2. Methods

2.2.1. Groups

According to the random number table, patients were randomly divided into the Tongxinluo capsule treatment group or the placebo group. Each group had 28 patients. The two groups showed no significant difference in age, sex, blood glucose, blood lipid, blood pressure, SADS and SDS scores, 6-minute walk index test, exercise test, serum endothelin-1 levels and nitric oxide levels ($P > 0.05$).

2.2.2. Scale Scoring Method

SAS scale: The total score was multiplied by 1.25 to achieve the standard score, with a critical value of 50 points. A higher score indicated a higher degree of surface anxiety. SDS scale: the total score was multiplied by 1.25 to achieve the standard score, with a critical value of 50 points. A higher score indicated a more serious degree of depression.

2.2.3. Research Method

The Tongxinluo treatment group was given diltiazem capsules (Shanghai Xinyi Vientiane Pharmaceutical Limited, by Share Ltd. production), 30 mg three times

Table 1. Comparison of Sociodemographic data in two groups.

Project stratification	Tongxinluo group (case)	Control group (case)
male/female (case)	8/20	8/20
age < 55	8	10
55 < age < 70	20	18
farmer	3	2
worker	12	15
Professional and technical personnel	13	11
Degree of education: primary school	3	4
Middle school	7	9
Higher school	15	13
University and above	3	2

There is no significant difference between the two groups.

Table 2. Comparison of clinical characteristics data in two groups.

Project stratification	Tongxinluo group	Placebo Control group
Heart rate (beats/minute)	72 ± 12	67 ± 15
Blood pressure (mmHg)	$133/76 \pm 32/16$	$139/80 \pm 28/12$

There is no significant difference between the two groups.

a day, and Tongxinluo capsules (Shijiazhuang Yiling pharmaceutical production), 4 tablets three times a day, for a duration of 12 weeks. The placebo control group was given diltiazem capsules, 30 mg three times a day. The 6-minute walking test and exercise plate test were performed before and after the treatment. The exercise plate test was carried out using the MAX-1 plate motion tester and the Bruce program in the United States. After the treatment, the Self-Rating Anxiety Scale and the Self-Rating Depression Scale were evaluated. Two millilitres of venous blood was extracted on an empty stomach before and after the treatment. It was then centrifuged at 3000 r/min for 10 min, after which nitric oxide was detected by the nitrite method and (kit purchased from Shenzhen Jing Mei science and Technology Company). Endothelin-1 was determined by radioimmunoassay (kit purchased from Beijing East Asian immunology Institute). All of the above operations were carried out in strict accordance with the instructions of the kits.

3. Statistic

SPSS22 statistical software was used to analyze the data. The data were expressed as $\bar{x} \pm s$ data of the two groups were analyzed with the t test. Differences were considered when $P < 0.05$, and significant when $P < 0.01$.

4. Discussion

The results (Tables 3-5) of this study suggest that patients with Syndrome X have a higher proportion of Affective Disorders, which may be associated with the higher proportion of women affected. This study found that the age distribution of patients is 50 ± 16 , which is within the range of perimenopausal age.

Table 3. Comparison of SAS and SDS scores in two groups of patients before and after treatment.

Self-rating scale (score)	Tongxinluo group ($n = 28$)		Control group ($n = 28$)	
	Before	After	before	after
SAS	59 ± 4.9	$50 \pm 5.5^{**}$	57 ± 5.6	55 ± 6.2
SDS	56 ± 5.2	$47 \pm 6.1^{**}$	55 ± 5.3	56 ± 9.3

Note: Compared with pre-treatment of Tongxinluo group and control group. $^{**}P < 0.01$.

Table 4. Comparison of walking distance and exercise load electrocardiogram between two groups of patients before and after treatment.

Exercise tolerance	Tongxinluo group ($n = 28$)		Control group ($n = 28$)	
	before	after	before	after
6-minutewalk distance (meters)	463 ± 23	$490 \pm 35^{**}$	465 ± 26	470 ± 27
Plat motion time (min)	6.6 ± 2.9	6.9 ± 3.3	6.8 ± 3.0	6.6 ± 3.2
ST lower than 0.1 mv time (min)	2.0 ± 0.8	1.9 ± 0.6	2.3 ± 1.2	2.2 ± 1.0

Note: Compared with pre-treatment of Tongxinluo group and control group. $^{**}P < 0.01$.

Table 5. Comparison of serum endothelin-1 and nitric oxide level in two groups before and after treatment.

Vascular endothelial function	Tongxinluo group (<i>n</i> = 28)		Control group (<i>n</i> = 28)	
	before	after	before	after
ET-1 (ng/L)	49.3 ± 16.9	42.8 ± 12.8**	46.3 ± 13.3	47.2 ± 18.1
NO (μmol/L)	42.7 ± 9.2	52.2 ± 10.6**	43.8 ± 10.8	45.2 ± 9.6

Note: Compared with pre-treatment of Tongxinluo group and control group. ***P* < 0.01.

Presumably, it may be related to the poor regulation of the autonomic nerves in this part of the patient. Previous studies suggested that the regulatory dysfunction of the vagus nerve may be involved in the pathogenesis of the vagus [7]. In addition, unlike the evaluation of anxiety and depression in cardiovascular patients who have always been highly concerned, Syndrome X patients with anxiety and depression have not attracted enough attention from clinicians. Presumably, clinicians generally believe that the harm of the disease and mortality rate are low [8] [9] [10]. The symptoms do not attract a doctor's attention until the patient repeatedly presents with chest tightness, symptoms of chest pain and discomfort, complaints of daily work, sports and life being seriously affected, and the requirement of repeated hospitalizations. The SAS and SDS, as two self-rating scales, are easy to operate and grasp. They are widely used in the evaluation of patients with cardiovascular disease, and clinical studies suggest that they have a good correlation with the hospital anxiety and depression subscale. This study suggests that patients can complete the self-evaluation of anxiety and depression according to the tabular presentation. The data suggest that the proportion of patients with anxiety and depression is higher, and that most of them have mild anxiety and depression, which may be related to the small sample size and lack of multiple evaluation tools.

In addition, the current research on the pathogenesis of cardiac Syndrome X suggests that coronary microvascular dysfunction is an important pathogenesis. Endothelial dysfunction plays an important role in patients with cardiac Syndrome X. Research suggests that these patients showed decreased synthesis and release of nitric oxide, while endothelin-1 release increased, which led to vascular endothelial dysfunction, coronary flow reserve and impaired motility disorders. This affects the micro-arterial circulation, causing myocardial ischaemia and angina, clinically detected as a positive exercise load electrocardiogram test and exercise radionuclide filling defects [11]. Commonly used drugs, such as nitrates, can alleviate the occurrence of chest pain but are unable to increase activity tolerance. Beta receptor blockers not only reduce skeletal muscle blood flow but also increase the risk of patients with Affective Disorder and are not as good at treating exertional angina. Clinical doctors have abandoned this drug; therefore the treatment of the disease by clinical medicine is limited. Clinical findings regarding the use of calcium antagonists indicate they can reduce the degree and frequency of Syndrome X exacerbations in patients with chest pain syndrome

and showed an increased activity tolerance, similar to this study. However, some patients cannot tolerate the gastroesophageal reflux, which brings difficulty to its clinical application.

The Tongxinluo capsule is a compound preparation of traditional Chinese medicine, with main components of ginseng, leech, scorpion, red peony root, cicada, wood louse insects, centipedes, sandalwood, and spinosae. Clinical research indicates that Tongxinluo capsule therapy has the effect of activating blood and dredging collaterals and acts as an antispasmodic and analgesic. It has been widely used in the treatment of patients with coronary heart disease and cerebral infarction, and clinical study suggests that the Tongxinluo capsule can improve vascular endothelial function in many ways. This study found that it could increase the level of serum nitric oxide and reduce the level of serum endothelin-1, which is consistent with previous studies [12] [13] [14]. Nitric oxide is a bioactive substance synthesized by vascular endothelial cells and is a strong vasodilator and inhibitor of platelet adhesion and aggregation. Endothelin-1 is a vasoconstriction factor secreted from vascular endothelial cells. Nitric oxide acts to the contrary, and imbalance between the mediators can cause endothelial dysfunction, resulting in microcirculation. Patients who took Tongxinluo showed a decreased degree of chest pain and increased activity tolerance, which may be partially attributed to the improvement of endothelial function and the normalization of the microcirculatory system.

It is worth noting that, compared to the placebo group, patients in the Tongxinluo treatment group had less frequency and degree of chest during the 12 weeks of treatment. In addition, after the therapy, the group showed significant improvement in depression and anxiety. It is presumed that this result may be related to the inclusion of sandalwood and *Zizyphus spinosa*. Sandalwood has a calming and tranquilizing effect. It can soothe nervous tension and anxiety, and the effect of the calmness is superfluous. The *Zizyphus spinosa* has a tranquilizing effect and is clinically used in the treatment of dysphoria insomnia and patients with sleep disorders [15]. In addition, the study found that the Tongxinluo treatment group had an increased 6-minute walking distance and activity tolerance, while the exercise load electrocardiogram showed no significant difference between the two groups. This indicates that Tongxinluo may be associated with improved Affective Disorder, and patients return to increased confidence in their daily lives.

5. Conclusion

In summary this study suggests that the Tongxinluo capsule has a significant therapeutic effect on patients with Syndrome X with anxiety and depression. In addition to improving the vascular endothelial function of patients, it can also reduce the degree of anxiety and depression, further increase exercise tolerance, reduce the times of outpatient visits and hospitalization, and increase the confidence of returning to work and normal life. Fortunately, no serious adverse re-

actions occurred during the study. However, the sample size was small; the period of treatment and observation was short, and no blank control group was set up. This may have a certain effect on the results of the study.

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