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Clinical Experience

Effect of Shexiang Tongxin Dropping Pills (麝香通心滴丸) on the Immediate Blood Flow of Patients with Coronary Slow Flow*

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ABSTRACT **Objective**: To observe the immediate effect and safety of Shexiang Tongxin dropping pills (麝香通心滴丸, STDP) on patients with coronary slow flow (CSF), and furthermore, to explore new evidence for the use of Chinese medicine in treating ischemic chest pain. **Methods**: Coronary angiography (CAG) with corrected thrombolysis in myocardial infarction (TIMI) frame count (CTFC) was applied (collected at 30 frames/s). The treatment group included 22 CSF patients, while the control group included 22 individuals with normal coronary flow. CSF patients were given 4 STDP through sublingual administration, and CAG was performed 5 min after the medication. The immediate blood flow frame count, blood pressure, and heart rate of patients before and after the use of STDP were compared. The liver and kidney functions of patients were examined before and after treatments. **Results**: There was a significant difference in CTFC between groups (P<0.05). The average CTFC values of the vessels with slow blood flow in CSF patients were, respectively, 49.98±10.01 and 40.42±11.33 before and after the treatment with STDP, a 19.13% improvement. The CTFC values (frame/s) measured before and after treatment at the left anterior descending coronary artery, left circumflex artery, and right coronary artery were, respectively, 48.00±13.32 and 41.80±15.38, 59.00±4.69 and 50.00±9.04, and 51.90±8.40 and 40.09±10.46, giving 12.92%, 15.25%, and 22.76% improvements, respectively. The CTFC values of vessels with slow flow before treatment were significantly decreased after treatment (P<0.05). There were no apparent changes in the heart rate, blood pressure, or liver or kidney function of CSF patients after treatment with STDP (all P>0.05). **Conclusions**: The immediate effect of STDP in treating CSF patients was apparent. This medication could significantly improve coronary flow without affecting blood pressure or heart rate. Our findings support the potential of Chinese medicine to treat ischemic chest pain.

KEYWORDS coronary artery, slow blood flow, Shexiang Tongxin dropping pills, Chinese medicine, ischemic chest pain

Coronary slow flow (CSF) is a special phenomenon seen while performing coronary angiography (CAG) on chest pain patients speculated to have coronary heart disease. Delayed blood perfusion in the distal coronary artery is found in patients without stenosis or with less than 40% stenosis in the epicardial coronary artery.[1] As the CAG technologies have become more pervasive, the discovery and diagnosis of CSF in patients have also increased. For some patients, the slow flow is not explained by coronary stenosis. Additionally, the blood perfusion in the distal coronary artery cannot be improved by percutaneous coronary intervention (PCI). In clinical practice, cardiovascular events are frequent in CSF patients; myocardial infarction and sudden death can even develop.[2] Kurtoglu, et al[3] performed CAG on 1,741 patients speculated to have coronary heart disease, and 5.5% of the patients had CSF. It has been more than 40 years since the first report on CSF by Tambe et al. However, the onset mechanism of CSF remains unclear. Moreover, there is no commonly agreed-upon treatment nor effective medication. The definition of coronary heart disease given in the 2013 European Society of Cardiology Guidelines on the management of stable coronary artery disease greatly differs from that given in the past.[4] The definition used to be simply based on the perspective of coronary stenosis. The updated

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definition was extended to cover microvascular dysfunction and coronary artery spasm as well as the inclusion of coronary microvascular disease in ischemic heart disease. However, there is no standard definition of CSF. Based on the studies on coronary microcirculation and slow flow[5-8] and the evidences supporting the potential of Chinese medicine in the treatment of heart diseases,[9,10] the authors treated 22 CSF patients with Shexiang Tongxin dropping pills (麝香通心滴丸, STDP), which are typically used to treat the chest pain caused by coronary heart diseases.

METHODS

CSF Diagnosis Criteria

(1) CAG results indicated no apparent lesion in the epicardial coronary artery. (2) The measured corrected thrombolysis in myocardial infarction (TIMI) frame count (CTFC) was no less than 27 frames/s for any single and/or multiple major coronary arteries, e.g. left anterior descending artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA).[1,11]

Inclusion Criteria

The subjects were admitted to the Cardiovascular Center of the Ningbo First Hospital for chest pain between September 2013 and December 2014. Electrocardiograph (ECG) was used to detect myocardial ischemia in some patients. If coronary heart disease was considered, CAG examination was performed. The results indicated no apparent lesion in the epicardial coronary artery. Twenty-two patients satisfied the CSF diagnosis criteria, and 22 patients who showed no CSF were included as the control group. Detailed medical history was recorded for all subjects. The regular physical examination and the Seattle Angina Questionnaire were given to evaluate patient conditions.[12] Complete blood count, biochemical examination, ECG, and color Doppler echocardiography were performed. The patients were informed of the examination procedure and steps. Patient and family consent was obtained. All participants signed the informed consent. Our study was approved by the Institutional Review Board of the Ningbo First Hospital, China (2014-R013).

Exclusion Criteria

Patients with any of the following conditions were excluded: apparent stenosis found in the coronary arteries, coronary artery embolism, coronary artery spasm, coronary dissection, coronary dilatation, heart valve disease, myocardial bridge, cardiomyopathy, acute myocardial infarction within 3 months, frequent ventricular arrhythmia, left or right ventricular dysfunction, active liver disease, thyroid dysfunction, connective tissue disease, acute or chronic kidney diseases, currently receiving treatments of glucocorticoid and such, and allergy to either the content of STDP or the contrast agent.

Grouping

CSF group: The 22 patients who satisfied the CSF diagnosis criteria were included. Among the 22 patients, there were 17 males and 5 females with an average age of 58.8±9.1 years. One of the patients was complicated with diabetes, while 8 were accompanied by hypertension.

Control group: There were 22 patients in the control group; the CTFC values of the coronary arteries of these patients were all < 27 frames/s. Among these 22 patients, there were 15 males and 7 females with an average age of 57.1±11.2 years. Four of the patients were complicated with diabetes, while 11 of them were accompanied by hypertension.

Medication

STDP is a approved prescription medicine (approval No. Z20080018) by State Administration for Market Regulation (SAMR). STDP are manufactured by the Inner Mongolia Conba Pharmaceutical Co., Ltd. (35 mg per pill; product lot number 130708115).

Instruments

An Allura Xper FD20 digital subtraction angiography system (Philips, Netherlands) was used. The digital subtraction angiograph was integrated with a computer-assisted quantitative measurement tool.

Selective CAG and CTFC Calculations

Selective CAG was performed using a multifunctional 5F angiographic catheter via the standard percutaneous radial artery approach. During the angiography and 48 h prior to the operation, the uses of nitrates and other vasoactive drugs were forbidden. CAG was performed with patients in the normal imaging position, and the imaging speed was 30 frames/s. During the operation, a contrast agent was infused with a fixed speed of approximately 3 mL/s. For each position, images were collected for 3–5 cardiac cycles.

Quantitative sequential CAG (at 30 frames/s)

and analysis software were employed. The number of frames needed for the contrast agent to transfer from the beginning of the coronary artery to the distal end at the anatomical landmark was recorded. The obtained frame counts were then treated according to the Gibson's method.[11] Due to anatomical factors, the CTFC value of the LAD was obtained by dividing the frame count by 1.7. For the other two arteries, the CFTC values were equivalent to the frame counts. CAG for all patients was performed by one experienced cardiologist. Image reading and counts were performed by two experts trained for cardiovascular intervention who did not participate in the experiments. The average of the values obtained by these two experts was calculated.

Experimental Procedure and Observation Indicators

CAG was performed for CSF patients. The heart rate and blood pressure illustrated on the ECG monitor after the first CAG operation were recorded. The patients were given 4 STDP through sublingual administration. The changes in blood pressure and heart rate at 5 min after the medication were recorded. CAG was repeated to collect CTFC values. Liver and kidney functions were re-examined 24 h after CAG operation.

Statistical Data Analysis

SPSS18.0 was employed to process the data collected in our study. CTFC values are all expressed in the format of mean ± standard deviation ($\bar{x} \pm s$). The paired *t*-test was applied, and $P<0.05$ indicates that a difference was statistically significant.

RESULTS

General Information of the Two Groups

There were no significant differences ($P>0.05$) between the two groups in the following items: sex, incidence rate of hypertension, incidence rate of diabetes, age, systolic and diastolic blood pressure, heart rate, total cholesterol, low-density lipoprotein, triglycerides, fasting blood glucose, serum creatinine, and blood urea nitrogen (Table 1).

Table 1. Comparison of Clinical Data between the Two Groups

Indexes	Treatment Group (*n*=22)	Control Group (*n*=22)	*P* value
Gender [male (%)]	17 (77.3)	15 (68.2)	0.458
Age (Year, $\bar{x} \pm s$)	58.8 ± 9.1	57.1 ± 11.2	0.659
Smoking [Case (%)]	10 (45.5)	8 (36.4)	0.376
Hypertension [Case (%)]	10 (45.5)	11 (50.0)	0.095
Diabetes [Case (%)]	1 (4.5)	4 (18.2)	0.342
Systolic Pressure (mm Hg, $\bar{x} \pm s$)	118.45 ± 14.73	125.68 ± 15.87	0.125
Diastolic Pressure (mm Hg, $\bar{x} \pm s$)	79.36 ± 12.78	74.31 ± 13.83	0.216
Heart Rate (beat/min, $\bar{x} \pm s$)	70.77 ± 9.85	69.95 ± 8.38	0.768
TC (mmol/L, $\bar{x} \pm s$)	4.15 ± 1.09	4.15 ± 0.97	0.985
LDL (mmol/L, $\bar{x} \pm s$)	2.40 ± 0.67	2.68 ± 0.62	0.148
TG (mmol/L, $\bar{x} \pm s$)	1.83 ± 1.22	1.57 ± 1.11	0.465
GLU (mmol/L, $\bar{x} \pm s$)	4.44 ± 0.70	4.98 ± 1.15	0.071
Cr (μmmol/L, $\bar{x} \pm s$)	70.06 ± 15.13	66.01 ± 11.43	0.323
BUN (mmol/L, $\bar{x} \pm s$)	5.23 ± 1.43	5.24 ± 0.99	0.977

Notes: TC: Total cholesterol; LDL: low density lipoprotein; TG: triglyceride; GLU: glucose; Cr: creatinine; BUN: blood urea nitrogen; $P<0.05$ was considered to indicate a statistically significant difference.

Research Results of CFTC

Among the 22 CSF patients, a total of 30 blood vessels showed various degrees of delayed blood perfusion. There were 16 patients (72.7%) with 1 affected vessel, 4 (18.2%) with 2 affected vessels, and 2 (9.1%) with 3 affected vessels, which composed, respectively. The slow-flow vessels included 15 LAD, 4 LCX, and 11 RCA, which composed 50.0%, 13.3%, and 36.7% of the affected vessels, respectively.

The average CFTC values measured at the LAD, LCX, and RCA of patients in the CSF group were greater than those of the subjects in the control group ($P<0.01$, Table 2).

Table 2. Comparison of CTFC Value between Two Groups (Frame/s, $\bar{x} \pm s$)

Indexes	Case	Mean CTFC	LAD	LCX	RCA
Control	22	22.61 ± 1.65	23.24 ± 2.84	22.18 ± 2.99	22.45 ± 2.59
Treatment	22	49.98 ± 10.01*	48.00 ± 13.32*	59.00 ± 4.69*	51.90 ± 8.40*

Notes: CTFC: corrected TIMI frame counted; LAD: left anterior descending; LCX: left circumflex coronary artery; RCA: right coronary artery; *$P<0.01$, compared with the control group

In the CSF group, the CTFC values obtained after sublingual administration of STDP were less than those before the medication ($P<0.05$, Figure 1).

Effects of STDP on the Blood Pressure and Heart Rate of CSF Patients

After STDP were given through sublingual administration, the heart rate and blood pressure of CSF patients were all within the normal range. Compared with data taken before medication, the differences were not statistically significant (Table 3).

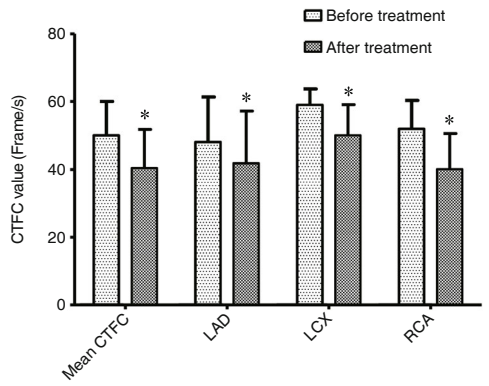

Figure 1. Comparison of CTFC Value before and after Treatment in the CSF Group

Notes: TIMI: thrombolysis in myocardial infarction; CTFC: corrected TIMI frame counted; LAD: left anterior descending; LCX: left circumflex coronary artery; RCA: right coronary artery; *P<0.05, compared with before treatment.

Table 3. Comparison of Blood Pressure and Heart Rate before and after Treatment in CSF Patients ($\bar{x} \pm s$)

Indexes	Case	Heart rate (beat/min)	Systolic pressure (mm Hg)	Diastolic pressure (mm Hg)
Before treatment	22	70.77±9.84	118.45±14.72	79.36±12.78
After treatment	22	70.23±8.97	120.09±11.91	78.27±10.67
P value		0.574	0.345	0.447

Effects on the Liver and Kidney Functions and Adverse Effects

After STDP were given through sublingual administration, the alanine transaminase, aspartate transaminase, blood urea nitrogen, and creatinine levels of CSF patients were all within the normal ranges. Compared with before medication, the differences were not statistically significant (data not shown). Two patients experienced tongue numbness. No other adverse reactions occurred.

DISCUSSION

CAG is the gold standard in the diagnosis of coronary heart disease. It is commonly agreed among cardiologist that coronary heart disease is not considered if CAG does not show coronary artery stenosis in the patients. However, "X syndrome" and the CSF phenomenon were discovered along with a better understanding of coronary heart disease. Ischemic heart diseases should include obstructive and non-obstructive coronary artery lesions. Most researchers agree that CSF should be considered as a non-obstructive coronary artery lesion. Abnormal blood flow in the coronary artery can be divided into two categories.[13] One is CSF phenomenon, which should be considered primary CSF. Its onset mechanism remains unclear and is the subject of our study. The other type of slow blood flow is considered secondary, and it has clear causes, such as PCI-related factors, coronary artery spasm, and microthrombus. These diseases cause the reduction of blood flow in the coronary artery and increase the blood flow resistance in peripheral blood vessels. Moreover, the following conditions may occur: microcirculation block, increased intravascular pressure, reperfusion and hemorheological injuries, increased left ventricular end-diastolic pressure, and tissue injury, which further reduce coronary blood flow.[14]

Most scholars agree that CSF is related to coronary microcirculation dysfunction and endothelial dysfunction. Gibson, et al[11] adapted myocardial biopsy and found that patients with CSF had a certain degree of edema, capillary injury, and shrunken microvascular lumen in the myocardial cells. Mangieri, et al[13] performed biopsy on the left ventricular myocardial cells of CSF patients; thickened microvascular lumen, narrowed microvascular lumen, abnormal mitochondria, and reduced glycogen were observed. Based on these findings, it is commonly agreed that CSF is related to coronary microvascular dysfunction which increases the resistance to forward blood flow.[13,14]

Endothelial dysfunction is another hypothesis for CSF. Some studies[15,16] found that the endothelin-1 (ET-1) level of CSF patients was higher than that of the control group. Additionally, the serum nitric oxide (NO) level of CSF patients was lower than that of the control group and was negatively correlated with the blood flow speed. The authors[4,7] employed the dobutamine stress test to examine the changes in ET-1 and NO levels in CSF patients under stress. The results indicated that the imbalance between the two substances was even more visible when patients were under stress. Moreover, the myocardial perfusion insufficiency in CSF patients was further confirmed by ultrasound imaging of the hearts. Hence, an inference could be drawn from the data that the endothelial dysfunction in CSF patients is more dominant under stress, leading to more severe myocardial perfusion insufficiency and more significant manifestation of ischemia.

Gibson, et al[11] reported that based on the TIMI blood flow grades, increased the number of frames

(30 frames/s) during CAG and quantitatively analyzed the blood flow. Sadamatsu, et al[17] gave 11 patients sequential intracoronary injections of nitroglycerin and nicorandil; the effects of the different medications on improving slow blood flow in the same blood vessel were observed. As observed with CAG, the average CTFC value dropped from 43 frames to 32 frames after the injection of isosorbide dinitrate. Moreover, the CTFC value further decreased to 25 frames after intracoronary injection of 1 mg of nicorandil. The CTFC values obtained in the final re-examination returned to the initial counts. Ozdogru, et al[18] evaluated the effects of intracoronary injections of nitroglycerin and diltiazem on the CTFC values of CSF patients. The results indicated that these two medications could increase the coronary blood flow speed. Diltiazem performed better than nitroglycerin in improving the CTFC values measured at the LCX and LAD. Chang, et al[19] adopted intracoronary injections of nitroglycerin and verapamil; the performance of the two medicines in improving the blood flow in CSF patients was monitored. The results showed that these two medications could reduce the CTFC value to various degrees. Compared with the control group, the differences were statistically significant. The immediate effects of verapamil were better than those of nitroglycerin. However, the CTFC values obtained after the treatment did not reach the normal range.

Currently, the treatments for CSF mainly include enhancement of microcirculation, protection of the vascular endothelium, anti-inflammation action, and atherosclerosis inhibition. Chinese medicine can drastically improve the coronary microcirculation. In former studies by the authors, the combined use of STDP and statins relieved CSF and chest pain.[5] The potential of STDP in various diseases were previously reported.[20,21] Moreover, the sublingual administration of STDP did not change the basal heart rate or blood pressure of the patients and did not affect liver or kidney function. These results suggest that the sublingual administration of STDP allows for rapid absorption and rapid effects on the coronary microcirculation. This treatment is safe and effective in improving the coronary blood flow speed of CSF patients.

The potential of traditional medicine in the treatment of various diseases is increasingly recognized.[22-24] STDP is a new Chinese patent medicine that can be used to treat ischemic cardiovascular diseases. The pill is a representative medication for treating coronary heart disease by way of sputum-heat and blood stasis.

Wang, et al[25] provided data supporting the function of STDP in stabilizing atherosclerotic plaques. Zhang, et al[26] studied the function of STDP in protecting the vascular endothelium of rats during the early stage of injuries. The results suggested that injury to the vascular endothelium was reduced with the use of STDP. Moreover, blood NO gradually increased, while hypersensitive C-reactive protein and ET decreased. STDP improved the functions of improving coronary microcirculation, through protecting the vascular endothelium, producing anti-inflammation activity, and inhibiting atherosclerosis. The pill could specifically treat the main mechanisms of CSF—coronary microcirculation dysfunction and endothelial dysfunction. In our opinion, the rapid improvement in the blood flow of CSF patients after sublingual administration of STDP may be attributed to the effects of the pill in promoting microcirculation in the myocardial ischemic regions and improving regional blood supply. Therefore, the myocardial perfusion and myocardial ischemia in CSF patients were improved. The pharmaceutical mechanisms are unclear and require further investigation due to the small number of samples and lack of data on blood NO and ET levels before and after the treatment.

In summary, this study provides new information for treating ischemic chest pain. The results also show that sublingual administration of STDP allowed for rapid absorption and increased coronary blood flow speed. These data are critical in leading and guiding the treatments for coronary microvascular diseases and slow-flow complication after PCI. We believe that with more in-depth studies, STDP could play a critical role in the treatment of ischemic heart disease.

Conflict of Interest

The authors declare that they have no competing interests.

Author Contributions

Wang SH conceived and designed the experiments; Chu L, Xu Z, and Zhou HL performed the experiments; Chen JF and Ning HF analyzed the data. All authors drafted or revised the manuscript.

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