

# Clinical research investigating salvianolate injection for treating coronary angina pectoris of Qi blood stagnation

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Angina pectoris is a clinical syndrome that mainly presents with paroxysmal pectoralgia induced by sudden myocardial ischemia and hypoxia due to inadequate coronary blood flow from a narrow coronary artery. The disease is common among men >40 years of age and has a high attack rate. If it is not treated correctly, myocardial infarction and death may occur. Therefore, appropriate therapy is highly important to clinical prognosis. Coronary artery disease is characterized by chest discomfort and pain in traditional Chinese medicine. Regulating vital energy, reducing phlegm,

onyang and dredging collaterals are the primary treatment targets of Chinese herbs. Salvianolate is used for treating this disease, but its components are so complex that its purity is difficult to control. In recent years, research has found that depside salts from *Salvia miltiorrhiza* are the crucial effective components that have shown apparent effects in antioxidation, anticoagulation, cytoprotection and antiaging, among others. For the past few years, depside salts of *Salvia miltiorrhiza* in lyophilized powder form for injection have been used for adjuvant therapy to treat coronary angina pectoris of Qi blood stagnation.

**Key Words:** *Coronary angina pectoris; Qi-blood stagnation; Salvianolate*

## METHODS

Eighty-one patients (56 male, 25 female; mean [± SD] age 58.6 years [range 42 to 73 years]) with coronary angina pectoris of Qi-blood stagnation, who were treated at the authors' hospital between January 2013 and June 2014 were chosen as subjects. The shortest course of disease was four months and 10 years was the longest (mean 4.4±1.2). All patients were randomly separated into a control group with 40 patients and treatment group with 41 patients. The control group consisted of 27 men and 13 women between 42 and 70 years of age (mean 59.2±8.5 years), the shortest course of disease was four months, the longest was nine years (mean 4.5±1.4 years). The treatment group included 29 men and 12 women between 45 and 73 years of age (mean 56.8±7.9 years), the shortest course of disease was six months, the longest was 10 years (mean 4.2±1.8 years). Differences in sex, age and disease course were not statistically significant ( $P>0.05$  [ $\chi^2$  test]).

### Inclusion criteria

The criteria should conform to diagnostic standard of integrative Chinese and western medicine for angina pectoris. Diagnostic standard of traditional Chinese medicine (TCM) for thoracic obstruction and judging standard of syndrome differentiation and syndrome in TCM are established by referring to Interpretation of Guideline for Clinical Study on thoracic obstruction (coronary heart disease and angina pectoris) treated with new TCM. The diagnostic criteria of Western medicine is established by referring to International Society of Cardiology and WHO standardization of clinical nomenclature Union Group Report – Nomenclature and Diagnostic Criteria for Ischemic Heart Disease (2). The cardiodynia severity classification criteria of thoracic obstruction is established by referring to treatment of angina pectoris and arrhythmia with combination of TCM and Western Medicine symposium – Angina pectoris and ECG curative effect standard in 1979. TCM is the study of the flow of Qi (energy) through the body;

blood stasis-type diseases are associated with chest tightness/fullness, impatient demeanor, a dark purple tongue and irregular heart rate.

### Exclusion criteria

Patients with acute myocardial infarction, severe arrhythmia, heart failure, severe neurosis, climacteric syndrome and chest pain caused by cervical spondylosis were excluded. Patients with lung, liver, kidney, hemopoietic system and other primary diseases and mental disorders were also excluded, as were women who were pregnant or lactating. Additionally, individuals who had undergone a recent surgery (within four weeks) and with bleeding tendency were excluded, as were patients who were allergic to this preparation, unwilling to be tested or whose data were missing.

### Therapy

**Control group:** Nitroglycerin, aspirin and statins were administered for secondary prevention of coronary artery disease to dilate the coronary artery and improve collateral circulation, inhibit platelet adhesion and aggregation, and stabilize atherosclerotic plaque, respectively. **Treatment group:** Based on the control group, 0.2 g salvianolate was added to 250 mL 5% glucose liquid for intravenous drip, once a day.

Both groups were treated two weeks for one course.

### Observation index

**Safety detection:** General parameters were investigated including blood, urine, and stool routine examination, liver and kidney function examination.

**Curative effect observation:** Attack frequency, pain intensity, duration, cause, dosage of nitroglycerin, stopped or decreased percentage of drugs to dilate coronary artery were observed (patients with exertional angina pectoris should be tested in the same activity when attack frequency, pain intensity, and duration were evaluated before and after treatment).

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**TABLE 1**  
Comparison of the curative effect between control and treatment groups

Groups	Cases	Excellent	Effective	Ineffective	Exacerbated	Total effective rate, %
Control	40	19	9	10	2	70.0
Treatment	41	28	9	4	0	90.2*

Data presented as n unless otherwise indicated. \*Compared with control group ( $P<0.05$ )

**TABLE 2**  
Comparison of electrocardiographic parameters between control and treatment groups

Groups	Cases	Excellent	Effective	Ineffective	Exacerbated	Total effective rate, %
Control	40	14	12	9	5	65.0
Treatment	41	18	17	6	0	85.4*

Data presented as n unless otherwise indicated. \*Compared with control group ( $P<0.05$ )

**TABLE 3**  
Comparison of stopped or decreased percentage of available drugs to dilate coronary artery between the two groups

Groups	Cases	Stopped	Decreased	Unchanged	Stopped or decreased, %
Control	40	18	14	12	70.0
Treatment	41	9	7	3	92.7*

Data presented as n unless otherwise indicated. \*Compared with control group ( $P<0.05$ )

**TABLE 4**  
Comparison of changes in attack frequency before and after treatment between the two groups

Groups	Cases, n	Before treatment	After treatment
Control	40	6.5±2.7	4.9±1.2 <sup>†</sup>
Treatment	41	6.4±2.4	2.1±1.0* <sup>†</sup>

Data presented as mean ± SD unless otherwise indicated. \*Compared with control group ( $P<0.05$ ); <sup>†</sup>Compared with previous treatment ( $P<0.05$ )

The changes of TCM syndrome characteristics, tongue and heart rate condition were also observed. Electrocardiography (ECG) and exercise test were performed before and after therapy.

#### Judgment of curative effect

The standard were formulated by referring to Interpretation of Guideline for Clinical Study on thoracic obstruction (coronary heart disease and angina pectoris) (2) and treatment of angina pectoris and arrhythmia with combination of TCM and Western medicine symposium- Angina pectoris and ECG curative effect standard in 1979 (3). The treatment was excellent if the dose of nitroglycerin was reduced by >80%, attack frequency in the same activity reduced by >80% or attacks were not found. The treatment was effective if attack frequency and dosage of nitroglycerin were reduced by 50% to 80%, the pressure of ST segment at rest recovered to >1.5 mm and T wave was positive. The treatment had no effect if attack frequency and dosage of nitroglycerin was reduced by <50% and changes of EGG in ST-T segment were not observed. Illness was exacerbated if dosage of nitroglycerin, attack frequency and its severity increased and duration was prolonged.

$$\text{Total effect rate (\%)} = (\text{excellent ones} + \text{effective ones}) / (\text{all}) \times 100$$

## RESULTS

#### Comparison of curative effect between the two groups

The curative effect of improving angina in treatment group was superior to the control group and differences between two groups were statistically significant (ie,  $P<0.05$ ) using the Ridit test. Results are summarized in Table 1.

#### Comparison of EGG between the two groups

The curative effect of improving EGG in the treatment group was superior to the control group and differences between two groups were statistically significant ( $P<0.05$ ) using the Ridit test. Results are summarized in Table 2.

**TABLE 5**  
Comparison of symptom interval between the two groups

Groups	Cases, n	Before treatment	After treatment
Control	40	15.6±2.8	9.3±2.5 <sup>†</sup>
Treatment	41	16.3±3.8	6.0±3.1* <sup>†</sup>

Data presented as mean ± SD unless otherwise indicated. \*Compared with control group ( $P<0.05$ ); <sup>†</sup>Compared with previous treatment ( $P<0.05$ )

#### Comparison of stopped or decreased percentage of available drugs to dilate the coronary artery between the two groups

The differences of stopped or decreased percentage of available drugs to dilate coronary artery between two groups were statistically significant ( $P<0.05$ ) according to the Ridit test. Results are summarized in Table 3.

#### Comparison of changes in attack frequency before and after treatment between the two groups

By *t* test of two sample means, attack frequency reduced apparently within group before and after treatment ( $P<0.05$ ), and differences were statistically significant ( $P<0.05$ ) after treatment between the two groups. Results are summarized in Table 4.

#### Comparison of symptom interval between two groups

By *t* test of two sample means, symptom interval was obviously decreased before and after treatment within group and the differences were statistically significant ( $P<0.05$ ) after treatment between the two groups. Results are summarized in Table 5.

#### Results of safety detection

No adverse reactions were reported during treatment between the two groups, nor was there apparent liver and kidney function damage before and after administration.

## DISCUSSION

Angina pectoris, whose common type is Qi-blood stagnation type is one of chest congestion in TCM. The main cause of this type of angina is damage due to an excess of seven emotions. The heart governs the mind and blood circulation, liver stores of blood and controls catharsis. There is close relationship between the two. Only if liver function is normal can Qi-blood of the heart can be calm. For elderly individuals, who lack Qi-blood, yin and yang of the heart, spleen and kidney, are cold invasioned, consume an inappropriate diet, have emotional

disorders and excessive fatigue, among others, can also lead to blood stasis stagnation, which can consequently cause coronary angina pectoris of Qi-blood stagnation. The 'Suwen•Yujizhenzang' theory has described "blockage of vessel, inability of Qi to flow freely", which illustrates that blood stagnation can lead to Qi depression (4). Therefore, accelerating blood circulation, removing blood stasis and promoting the circulation of Qi are the main therapies.

*Salvia miltiorrhiza*, which can dilate the coronary artery, improve collateral circulation, promote opening of the capillary network, increase coronary blood flow, prevent myocardial ischemia and infarction, reduce myocardial contraction, oxygen consumption, cholesterol, inhibiting cruor and activate fibrinolysis. It is a common drug for invigorating blood circulation and eliminating stasis in clinical TCM. However, its components are so complex that its purity difficult to control. Depside salts of *Salvia miltiorrhiza* in lyophilized powder form for injection have hydrosoluble effective components and it has stable quality and few adverse reactions. Its mechanism of protecting against myocardial ischemia is described as follows: a) Platelet adhesion and aggregation are the main reason of arterial thrombosis in highly condensed state, while significant research has proven that depside salts from *Salvia miltiorrhiza* can reduce p-selectin and effectively inhibit platelet aggregation induced by EP and ADP. b) The main factor of atherosclerosis is oxidized low-density lipoprotein (Ox-LDL). Depsides salts from *Salvia miltiorrhiza* can apparently

resist LDL oxidation mediated by CU and endothelial cells owing to an oxidizability greater than vitamin C. Therefore, it can inhibit the generation and development of atherosclerosis. c) Salvianolic acid A promotes the formation of intracellular ATP and improves mitochondrial oxidative phosphorylation dysfunction to protect cardiac myocyte damage induced by hypoxia and improves arrhythmia induced by reperfusion by inhibiting intracellular calcium increasing and free radical scavenging induced by ischemia-reperfusion injury. d) Depsides salts from *Salvia miltiorrhiza* promote angiogenesis via stimulating human monocytes to release VEGF, BFGF and endothelial cell migration. e) *Salvia miltiorrhiza* in lyophilized powder form for injection can increase the level of serum NO and SOD activity, decrease the level of MDA, LDH, CK, MB, inhibit their damage to myocardium and protect ischemia reperfusion cell (6,7).

Research results showed that depside salts from *Salvia miltiorrhiza* in lyophilized powder form for injection used for adjuvant therapy in coronary angina pectoris of Qi-blood stagnation had a significant effect, and total effective rate of both angina and ECG were prior to mere secondary prevention of coronary heart disease. Moreover, attack frequency and dosage of available drugs to dilate the coronary artery decreased drastically. Adverse reactions were not reported. What is illustrated above is that depside salts from *Salvia miltiorrhiza* in lyophilized powder form for injection in coronary angina pectoris of Qi-blood stagnation warrants clinical evaluation.

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