

Original Article

A Prospective Randomized Multicenter Controlled Trial on Salvianolate for Treatment of Unstable Angina Pectoris in A Chinese Elderly Population*

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ABSTRACT **Objective:** To evaluate the efficacy and safety of salvianolate in elderly patients with unstable angina pectoris (UAP). **Methods:** A prospective double-blind randomized placebo-controlled multicenter trial in elderly patients with UAP from 13 third-grade class-A hospitals in China was performed. A total of 318 patients were randomly allocated in a 1:1 ratio to an experimental group (160 patients) and a control group (158 patients). The experimental group was treated with salvianolate for 14 days on the basis of conventional medicine, and the control group was given a placebo for 14 days with the same criteria. Follow-up was lasted 28 days in both groups. The primary endpoint was biweekly frequency of angina pectoris attacks. The secondary endpoints included biweekly dosage of nitroglycerin, the Seattle Angina Questionnaire, angina pectoris severity and duration, myocardial injury markers, high-sensitivity C-reactive protein (hs-CRP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), as well as major adverse cardiovascular events (MACEs). Safety was assessed according to adverse events and serious adverse events. **Results:** Baseline characteristics were similar between treatment groups. Compared with those in the control group, the frequency of biweekly angina attacks (2.92 vs. 4.08, $P=0.025$), the biweekly dosage of nitroglycerin, as well as the severity and duration of angina attacks ($P<0.01$) were reduced by salvianolate. The Seattle Angina Questionnaire score was also significantly improved in the experimental group than in the control group ($P<0.05$). No significant differences were observed between the two groups with respect to the incidence of MACEs. Salvianolate was well tolerated. **Conclusions:** Salvianolate appear to have efficacy and well tolerated for elderly patients with UAP. [ClinicalTrials.gov identifier: NCT03037047]

KEYWORDS Salvianolate, unstable angina pectoris, elderly, efficacy

Unstable angina pectoris (UAP) is the most common clinical presentation of acute coronary syndrome (ACS). Conventional medications for UAP include aspirin, angiotensin-converting enzyme inhibitors, beta-blockers, calcium antagonists, and nitrates.⁽¹⁾ Despite treatment with conventional agents and/or revascularization, many angina patients remain symptomatic. One year after coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI), 25% to 60% of patients continue to

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have angina and require antianginal medication.⁽²⁻⁴⁾ In elderly patients, the situation is even worse. Ageing is considered a risk factor for UAP,⁽⁵⁾ and it is not easy to detect unstable plaques with the current detection techniques for elderly patients who are vulnerable to UAP and are often exposed to a lack of opportunity for coronary intervention and CABG surgery.⁽⁶⁾ As a result, intensive drug therapy is a better choice, and evaluation of the efficacy and safety of proper medication becomes urgent in elderly patients.

Salvia miltiorrhiza, a traditional medical herb known as Danshen, has been widely used in China to treat coronary heart disease (CHD). Salvianolate (also known as *Salvia miltiorrhiza* depside salt), a Chinese patent drug, is extracted from the dried root of *Salvia miltiorrhiza*. In 2005, salvianolate was approved by the China FDA and appeared on the market (License Number: Z20050248) in 2006 for the treatment of CHD. Salvianolate is a lyophilizing powder for infusion. It contains magnesium lithospermate B (MLB, $\geq 85\%$) and its analogs, namely, rosmarinic acid (RA) and lithospermic acid (LA), as active components.⁽⁷⁻⁹⁾ The concentrations of the active components are determined by fingerprint analysis using high performance liquid chromatography.^(10,11) The pharmacological effects of salvianolate and its active components have been extensively investigated. Experimental studies have demonstrated that MLB attenuates atherosclerosis and protects against myocardial ischemia-reperfusion injury. Mechanistic studies have shown that MLB achieves the above effects by free radical scavenging and antioxidant activity, prevention of endothelial dysfunction, anti-inflammatory effects and regulation of matrix metalloproteinase expression and activity, modulation of lipid profiles and potential immunomodulation. RA and LA also showed beneficial effects on the cardiovascular system.⁽¹¹⁾

Several clues suggest that salvianolate may be effective in treating UAP. An analysis was conducted using data from a multicenter, phase IV clinical trial undertaken in China that enrolled 2,150 patients hospitalized for stable angina from 50 hospitals. The trial demonstrated that the patients receiving salvianolate treatment had better response if they experienced three or more episodes of angina per week.⁽¹²⁾ A systematic review reported the combined use of salvianolate and Western medicine in the treatment

of UAP can achieve better effects.⁽¹³⁾ However, to date, limited data are available regarding the effects of salvianolate in elderly patients with UAP. The present study was designed to evaluate the improved effects of salvianolate in a high-risk population of elderly patients with UAP, including analyses of angina frequency, nitroglycerin consumption and quality of life, as well as safety by a multicenter randomized controlled study. We hypothesized that perioperative administration of salvianolate may improve onset of UAP compared with the standard procedure.

METHODS

Study Design and Population

The proposed study is a prospective, randomized, double-blind, multicenter, parallel-controlled clinical trial (ClinicalTrials.gov identifier: NCT03037047, Title: Efficacy and Safety of Salvianolate Injection in Elderly Patients with Unstable Angina Pectoris). Cases were collected in 13 Chinese hospitals (The General Hospital of the People's Liberation Army, Inner Mongolia People's Hospital, the Second Affiliated Hospital of Nanjing Medical University, the First Affiliated Hospital of Harbin Medical University, Tianjin First Central Hospital, Chongqing General Hospital, Shenyang Red Cross Hospital, Guangzhou First People's Hospital, Beijing Geriatric Hospital, the Second Affiliated Hospital of Heilongjiang University of Traditional Chinese Medicine, Guizhou Province Hospital of Traditional Chinese Medicine, the First Bethune Hospital of Jilin University, the First Affiliated Hospital of Wenzhou Medical University), and stratified and sectionalized random samples were adopted using a random number table according to the number of cases allocated and the random proportion of participating hospitals. The two groups were stratified and assigned equally with SAS software (SAS Institute, version 9.3) and made a random table with the block size of 4 by a statistician. Patients who satisfied the inclusion and exclusion criteria were randomly allocated in a 1:1 ratio to salvianolate (experimental) and control groups, through stratified randomization using the random number table in each study center by the investigators. It was a double blind study where neither the researchers nor the participant known if an individual was in the control group or was receiving the experimental medication. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local hospital ethics committee; informed consent was obtained from

each patient. The trial was designed following the guidelines of the Consolidated Standards of Reporting Trials (CONSORT).

The subjects eligible for this study were patients between the ages of 65 to 80 years with symptoms of UAP (including initial onset angina pectoris, progressive angina pectoris, nocturnal angina, postinfarction angina pectoris, angina decubitus, etc.).⁽¹⁴⁾ The subjects who had taken Chinese medicine (CM) to treat coronary disease were required to stop taking the medicine at least 1 week before the enrollment, and secondary prophylaxis for unstable angina was adopted.

The exclusion criteria were as follows: (a) patients with non-ST-segment elevation acute coronary syndromes (NSTEMI ACS) caused by nonatherosclerotic coronary artery disease (CAD) (e.g., arteritis, trauma, thromboemboli, cocaine abuse, complications attributable to interventional treatment of heart disease, etc.); (b) patients with angina pectoris caused by increased myocardial oxygen demand (e.g., aggravating activities, fever, tachycardia, high adrenaline levels, etc.); (c) angina pectoris induced by anemia, methemoglobinemia and hypoxemia; (d) thyroid dysfunction; (e) poor hypertension control (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg); (f) severe cardiac and pulmonary dysfunction; (g) severe arrhythmia; (h) hepatic, renal and hematopoietic systems exhibiting primary severe disease, with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels 3 times higher than the normal range and creatinine clearance rate (CrCl) ≤ 30 mL/min/1.73 m²; (i) patients who had a bleeding tendency after surgery within 4 weeks before the enrollment; (j) poor compliance with treatment and participation in other clinical trials; and (k) allergic constitution.

Sample Size Estimation

The estimated number of participants in each group was set at 144 by referring to the literature ($\beta = 0.1$, $\alpha = 0.05$, standard deviation = 7.8, $\delta = 3$), with the frequency of biweekly angina attacks as the primary outcome measure. However, considering a 10% drop-out rate and the need for block randomization, the planned enrollment for each group was ultimately decided to be 160 subjects, for a total of 320 subjects.

Drugs, Doses, and Courses of Treatment

Based on the clinical guidelines, patients were treated with conventional medicines for UAP. Conventional medicines are classified as anti-ischemic drugs, including nitrates, β -blockers, calcium-channel blockers, and angiotensin-converting enzyme inhibitors (ACEI); antiplatelet and anticoagulant drugs, including aspirin, clopidogrel, low-molecular-weight heparin (LMWH); and statins, among others.^(15,16) Medicines were used by clinicians according to specific clinical conditions.

Experimental drug: On the basis of conventional medicine, salvianolate (Shanghai Green Valley Pharmaceutical Co. Ltd., China, batch No.1509022) was used by intravenous infusion after being diluted with 250 mL normal saline, 30–40 drop/min, 200 mg once daily for 14 consecutive days.

Control drug: On the basis of conventional medicine, 30–40 drop/min, 250 mL normal saline (placebo) was administered by intravenous infusion once per day for 14 days.

Observation of Clinical Outcomes

Primary endpoint: Biweekly angina pectoris attacks (pretreatment, 14 days and 28 days after treatment).

Secondary endpoints: (1) Biweekly dosage of nitroglycerin (mg; pretreatment, 14 days and 28 days after treatment); (2) the Seattle Angina Questionnaire (SAQ), a 19-item self-administered questionnaire measuring five dimensions of coronary artery disease: physical limitation, anginal stability, anginal frequency, treatment satisfaction and disease perception. The SAQ was scored by assigning each response an ordinal value, beginning with 1 for the response that implies the lowest level of functioning, and summing across items within each of the five scales. Scale scores were then transformed to a 0 to 100 range by subtracting the lowest possible scale score, dividing by the range of the scale and multiplying by 100.⁽¹⁷⁾ (pre-treatment, 28 days after treatment); (3) information on angina symptoms: (a) severity of angina pectoris was evaluated by scoring as follows: before treatment, 14 days after treatment and 28 days after treatment. 0 score: none; 2 scores (mild): angina pectoris caused by physical activity that was more strenuous than the daily physical activity; 4 scores (moderate): angina pectoris caused by daily physical activity, which was slightly restrictive; 6 scores (severe):

physical activity lighter than daily activity caused angina pectoris, and daily activity was markedly limited. (b) duration of the angina pectoris attack: severity was evaluated by scoring as follows: before treatment, 14 days after treatment and 28 days after treatment. 0 score: none; 2 scores (mild): anginal pain attack usually lasting no more than 5 min; 4 scores (moderate): each time, persistent pain astring for more than 5 but less than 10 min; 6 scores (severe): pain astring for more than 10 min. (4) Major adverse cardiovascular events (MACEs), including myocardial infarction (MI), heart failure, emergency PCI, sudden cardiac death, and acute cerebral vascular events (during follow-up). (5) Myocardial injury markers (cardiac troponin T (cTnT), cardiac troponin I (cTnI), creatine kinase-MB (CK-MB), hypersensitive C-reactive protein (hs-CRP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) content (pretreatment, 14 days after treatment and 28 days after treatment). (6) Electrocardiography and echocardiography changes (pretreatment, 14 days after treatment). (7) Safety analysis: blood, urine and stool routine, hepatorenal function, blood clotting and electrolyte contents (during follow-up).

Statistical Analysis

Statistical analysis was performed using SAS 9.4, and a *P*-value less than 0.05 was considered statistically significant. Continuous data were reported as the mean \pm standard deviation ($\bar{x} \pm s$) and were compared using Student's *t*-test and the paired *t*-test. Categorical data were expressed as percentages and compared by the Chi-square test or Fisher's exact test. The ranked data were tested by the Cochran-Mantel-Haenszel (CMH) Chi-square test.

RESULTS

Baseline Characteristics

From May 2016 to May 2018, of the 318 randomized subjects in the trial, a total of 315 patients had completed the study and were included in the statistical analysis, including 159 in the experimental group and 156 in the control group (Figure 1). The proportions of males in the experimental and control groups were 47.2% and 47.4%, respectively, with no statistical significance (*P*=0.962). The mean ages of the two groups were 73.6 years and 72.4 years, respectively, with no statistical significance (*P*=0.161). In addition, there was no statistical significance in comparison of baseline data, such as height, weight,

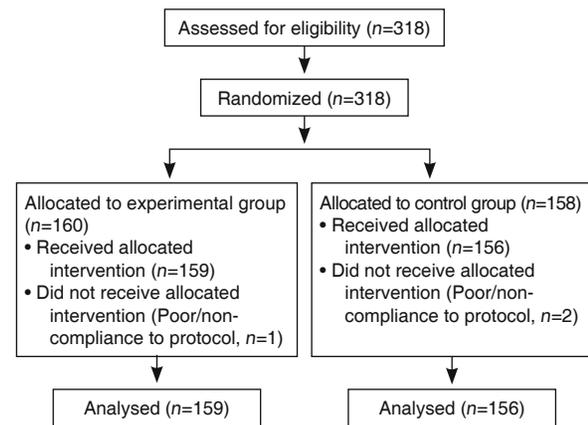


Figure 1. Flow Diagram of Patient Enrollment

Table 1. Baseline Clinical Characteristics of Two Groups

Item	Experimental group (n=159)	Control group (n=156)	<i>P</i> -value
Male [Case (%)]	75 (47.2)	74 (47.4)	0.962
Age (yr, $\bar{x} \pm s$)	73.6 \pm 7.9	72.4 \pm 7.9	0.161
Height (m, $\bar{x} \pm s$)	1.64 \pm 0.08	1.65 \pm 0.08	0.796
Weight (kg, $\bar{x} \pm s$)	66.1 \pm 10.2	65.9 \pm 10.2	0.852
Smoking [Case (%)]	30 (18.9)	43 (27.6)	0.067
Family history of CHD [Case (%)]	4 (2.5)	3 (1.9)	0.715
Diabetes [Case (%)]	62 (39.0)	55 (35.3)	0.493
Hyperlipidemia [Case (%)]	46 (28.9)	40 (25.6)	0.512
Hypertension [Case (%)]	112 (70.4)	116 (74.4)	0.437
MI [Case (%)]	16 (10.1)	14 (9.0)	0.756
Heart failure [Case (%)]	16 (10.1)	10 (6.4)	0.239
History of PCI [Case (%)]	28 (17.6)	24 (15.4)	0.595
History of CABG [Case (%)]	6 (3.8)	3 (1.9)	0.324
Biweekly angina pectoris frequency (Times)	9.45 \pm 11.12	8.39 \pm 9.13	0.358
Biweekly dosage of nitroglycerin (mg, $\bar{x} \pm s$)	2.00 \pm 2.86	1.77 \pm 2.42	0.849
Angina pectoris severity [Case(%)]			
Mild	70 (70.7)	63 (67.7)	
Moderate	0	0	0.136
Severe	28 (28.3)	21 (22.6)	
Angina pectoris duration [Case (%)]			
Mild	79 (49.7)	74 (47.4)	
Moderate	41 (25.8)	38 (24.4)	0.560
Severe	39 (24.5)	38 (24.4)	

Notes: CHD: chronic heart disease; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting

ethnic composition and marital status (Table 1).

Attack Frequency of Biweekly Angina Pectoris

At 14-day follow-up, the biweekly angina pectoris frequency in the experimental group and control

Table 2. Comparison of Seattle Angina Questionnaire Score between Groups ($\bar{x} \pm s$)

Group	n	Time	Seattle Angina Questionnaire score				
			Physical limitation	Anginal stability	Anginal frequency	Treatment satisfaction	Disease perception
Experimental	159	Pre-treatment	47.73 ± 20.14	26.26 ± 24.97	51.93 ± 27.50	48.65 ± 16.34	25.51 ± 15.26
		28-day post-treatment	57.19 ± 17.75* [△]	82.79 ± 22.96*	75.80 ± 22.92* ^{△△}	62.18 ± 11.70* ^{△△}	40.46 ± 12.52* ^{△△}
Control	156	Pre-treatment	46.84 ± 18.49	25.32 ± 23.59	52.25 ± 26.96	48.88 ± 15.00	26.04 ± 15.81
		28-day post-treatment	52.88 ± 18.08*	77.96 ± 23.36*	66.93 ± 27.99*	58.59 ± 11.64*	36.18 ± 14.68*

Notes: * $P < 0.01$, vs. pre-treatment in the same group; [△] $P < 0.05$, ^{△△} $P < 0.01$ vs. control group

group were 2.92 ± 4.10 and 4.08 ± 4.86 ($P=0.025$), respectively. At 28-day follow-up, the biweekly angina pectoris frequency in the experimental group (1.68 ± 2.69) was lower than that in the control group (2.36 ± 3.54), however, the differences were not statistically significant ($P=0.057$).

Biweekly Dosage of Nitroglycerin

During the follow-up periods of 14 and 28 days, the dosage of nitroglycerin in the experimental group was lower than that in the control group, which was 0.87 ± 2.18 mg vs. 1.28 ± 1.94 mg at 14 days ($P=0.006$), and 0.42 ± 1.51 mg vs. 0.68 ± 1.40 mg at 28 days ($P=0.006$), respectively.

Seattle Angina Questionnaire

There was no statistically significant difference between the two groups before treatment. At 28 days after treatment, four dimensions of SAQ score: physical limitation, anginal frequency, treatment satisfaction and disease perception were significantly higher in the experimental group than in the control group (Table 2). However, the anginal stability score did not reach the statistical difference at 28 days after treatment ($P=0.069$).

Angina Pectoris Severity

After 14 and 28 days of follow-up, the efficacy in the experimental group was better than that in the control group, and the difference was statistically significant ($P < 0.01$, $P < 0.05$, Table 3).

Duration of Angina Pectoris Attacks

During the follow-up periods of 14 and 28 days, the duration of angina pain attacks in the experimental group was significantly shorter than that in the control group, and the difference was statistically significant ($P < 0.01$, Table 4).

MACEs

Two cases of MACE occurred in the study: 1

Table 3. Comparison of Angina Pectoris Severity between Groups [Case (%)]

Group	n	Time	Angina pectoris severity			P-value vs. control group
			Mild	Moderate	Severe	
Experimental	159	Pre-treat.	70 (70.7)	0	28 (28.3)	0.136
		14-day post-treat.	50 (35.0)	0	2 (1.4)	<0.01
		28-day post-treat.	50 (34.2)	0	3 (2.1)	0.021
Control	156	Pre-treat.	63 (67.7)	0	21 (22.6)	
		14-day post-treat.	63 (49.2)	0	10 (7.8)	
		28-day post-treat.	53 (39.8)	0	9 (6.8)	

Table 4. Comparison of Angina Pectoris Duration between Groups [Case (%)]

Group	n	Time	Angina pectoris severity			P-value vs. control group
			Mild	Moderate	Severe	
Experimental	159	Pre-treat.	79 (49.7)	41 (25.8)	39 (24.5)	0.560
		14-day post-treat.	43 (27.7)	13 (8.4)	6 (3.9)	<0.01
		28-day post-treat.	44 (28.6)	10 (6.5)	1 (0.6)	<0.01
Control	156	Pre-treat.	74 (47.4)	38 (24.4)	38 (24.4)	
		14-day post-treat.	66 (43.1)	19 (12.4)	12 (7.8)	
		28-day post-treat.	54 (35.5)	11 (7.2)	12 (7.9)	

case (1/160) in the experimental group on the 7th day of follow-up and the other case (1/158) in the control group on the 14th day of follow-up, with no statistical significance. The case in the experimental group was recorded as MI with PCI, and the other case in the control group was recorded as non-ST-segment elevation MI with PCI. Both cases turned out well.

Myocardial Injury Marker, hs-CRP and NT-proBNP

There were no significant differences in CK-MB, hs-CRP, NT-proBNP, ST-segment change from electrocardiography and ejection fraction between the experimental group and the control group.

Safety and Tolerability

There were no clinically significant laboratory or physical examination abnormalities. Adverse events (AEs) occurred in 42/158 of the control group and 49/160 of the experimental group patients, and most were mild in severity. The most common AEs were dizziness, headache, palpitation, rash and itching. There was no significant difference in the incidence of AEs between the two groups. Few patients in either treatment group had serious adverse events (SAEs) (control group: 2/158; experimental group: 2/160); there was no significant difference in SAEs between the two groups. None of the SAEs were considered by the investigator to be drug-related. No deaths were reported during the study.

DISCUSSION

Agedness is an important risk factor for poor prognosis in patients with ACS.⁽¹⁸⁾ Considering the improvement of the prognosis, improving the quality of life in elderly patients should also be the core point. UAP is one of the relatively mild types of ACS; furthermore, the primary symptom in patients with CHD is angina pectoris. It is very valuable to reduce the intensity and duration of angina pain attacks to improve the quality of life of patients, especially for those who are reluctant to accept the intervention of arterial revascularization.

The drug for this study was salvianolate, which composed three active components (MLB [$\geq 85.0\%$], RA [$\geq 10.1\%$], and LA [$\geq 1.9\%$])⁽⁹⁾ with multiple biological activities, including attenuation of atherosclerosis and antioxidative damage, anti-inflammation, antiplatelet aggregation and endothelial protection, which could improve blood circulation and exert a myocardial protection effect.^(11,19,20) Thus, the potential value of the multiple targets of salvianolate is that its inclusion in a combination regimen may be more effective than that of conventional agents.

Angina is associated with symptoms experienced and worse health-related quality of life and is a major driver of repeat hospitalizations and increased healthcare costs.⁽²¹⁾ The accurate quantification of the frequency and severity of angina among patients with ischemic heart disease is critical for comparing treatment efficacy. Moreover, health status (symptoms, function, and quality of life) has been endorsed as an outcome-based performance measure

to assess healthcare quality in patients with ischemic heart disease.^(22,23) In this study, we evaluated the efficacy of salvianolate on UAP based on 3 criteria: frequency, severity and duration. The results of this study showed that the status in elderly patients with UAP was alleviated with the use of salvianolate, which provided a basis for improving angina symptoms. Moreover, salvianolate also reduced the nitroglycerin consumption. This finding is consistent with a previous cost-consequence retrospective study in 2,250 CHD patients that showed that compared with conventional treatment, salvianolate injection and conventional treatment led to a reduction of total nitrates dosage.⁽²⁴⁾

The SAQ is a self-administered, disease-specific health status questionnaire that measures clinically important dimensions of health in patients with ischemic heart disease. SAQ is sensitive to clinical change and could be a valuable measure of outcomes in cardiovascular research.^(17,22,25) In this study, salvianolate significantly improved the physical activity limitation, angina attack, satisfaction with treatment outcomes and degree of disease cognition as evaluated by the SAQ, which demonstrated that combined therapy with conventional medicine for elderly patients with UAP had an apparent advantage in quality of life improvement.

The use of combination therapy with multiple conventional agents should also be carefully monitored to avoid additive AEs. In our study, safety indicators such as liver and kidney function as well as myocardial injury markers were evaluated, and there were no significant differences in the incidence rates of AEs or SAEs between the two groups, suggesting that salvianolate is well tolerated in combination with conventional agents in elderly patients with UAP. These observation results are generally consistent with previous safety studies of salvianolate.^(26,27)

However, in this study, we found no difference between the two groups regarding the incidence of MACEs. A real-world study reported that among Chinese CHD and angina pectoris patients ($n=2,287$), those who used salvianolate had a lower cardiovascular event rate and spent less on cardiovascular event treatment during 1 year follow-up.⁽²⁸⁾ We speculated that the 28-day follow-up time was relatively short, and the short observation time in this study caused difficulty in evaluating the long-term outcomes. A long-

term follow-up study to clarify the effect of salvianolate combined with conventional medicine on MACE prevention is now in preparation.

In conclusion, we used a double-blind randomized placebo-controlled multicenter trial to demonstrate that salvianolate combined with conventional medications reduced the frequencies of angina and nitroglycerin consumption compared with those in the control group and was well tolerated in elderly patients with UAP. Therefore, we recommend using salvianolate together with conventional medications to improve short-term angina symptoms in elderly UAP patients.

Acknowledgments

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Conflicts of Interest

Shanghai Green Valley Pharmaceutical Co. Ltd. (Shanghai, China) provided the salvianolate and placebo. The Shanghai Green Valley Pharmaceutical Co. Ltd. had no participation or influence on the study design, data collection, statistical analysis, and interpretation of results.

Author Contributions

Li XY is the guarantor of this article and contributed to the conception of scope and protocol; provided supervision, coordination and guidance for collaborating, peripheral centers; conceived and implemented the analysis plan, and drafted the initial and final manuscript. Cui H, Gao XW, Lu X, Wu XP, Wang XF, Zheng XQ, Huang K, Liu F, Luo Z, Yuan HS, Sun G, Kong J, Du XH, Liu HY, Zheng J and Zhang WJ were responsible for data acquisition and took responsibility for the integrity of the data and the accuracy of the analysis. All authors have agreed and approved the final manuscript.

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