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Original Article

Addition of *Radix Salviae* Decoction for a Short Period Does Not Significantly Change Coronary Stenosis and Restenosis After Percutaneous Coronary Intervention: A Prospective Clinical Trial

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Abstract

Background and objectives: Restenosis is a serious complication for patients with coronary heart disease (CHD) undergoing percutaneous coronary intervention (PCI). In this prospective clinical study, we aimed to investigate the effects of *Radix Salviae* decoction (RSD) on coronary stenosis and restenosis in CHD patients.

Methods: We conducted this study at Guangdong Hospital of Traditional Chinese Medicine (registration No. BF2022-052) and enrolled 60 patients diagnosed with CHD for PCI surgery. The patients were divided into a control group and an RSD treatment group of 30 cases each. The primary outcome was restenosis after PCI, and the secondary outcome was newly increased stenosis (neostenosis).

Results: Fifty-eight of the 60 enrolled patients completed follow-up and were included in the final analysis, with 28 in the control and 30 in the RSD group. A baseline comparison of stenosis location, stenosis degree, and the number of vessels in stenosis before PCI showed comparable results ($p > 0.05$). Comparison of implanted stents showed similar features in stent diameter and stent length during PCI between the two groups ($p > 0.05$). For the primary outcome, there was no significant difference in restenosis percentage ($p > 0.05$) or the number of vessels in restenosis ($p > 0.05$) of the three arteries between groups. For the secondary outcome, neither the number of nonculprit vessels in neostenosis after PCI nor the percentage of neostenosis of the three arteries showed significant differences between groups ($p > 0.05$). Although multifactor logistic regression analysis for the incidence of restenosis did not find any statistically significant factors ($p > 0.05$), the diagnosis of MI/angina ($p = 0.031$), average stent length ($p = 0.010$), and alanine transaminase ($p = 0.027$) were found to be significantly associated with neostenosis occurrence. Safety index measurement indicated that RSD had a good safety profile in clinical treatment.

Conclusions: Although the addition of *Radix Salviae* decoction for a short period did not significantly change restenosis and neostenosis after PCI, the diagnosis of MI/angina, average stent length and aspartate aminotransferase levels were significantly associated with neostenosis occurrence. This pilot research will help to design future studies in investigating RSD effects on stenosis.

Keywords: Coronary heart disease (CHD); Percutaneous coronary intervention (PCI); *Radix Salviae* Decoction (RSD); Stenosis; Restenosis.

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Introduction

Coronary heart disease (CHD) refers to coronary atherosclerotic heart disease, a chronic inflammatory disease caused by lesions in the inner walls of the coronary arteries, resulting in insufficient blood supply to the heart and causing a series of symptoms and lesions. The main symptoms include angina pectoris, acute myocardial infarction, and arrhythmia, etc. The treatment of CHD is comprehensive, among which, percutaneous coronary intervention (PCI) is a fast and effective treatment to dilate the narrowed arteries and improve the blood supply to the heart. From the earliest days of balloon angioplasty to coronary stent placement and the use of drug-eluting stents (DES), PCI can reduce CHD symptoms and prevent myocardial infarction and other complications.[1]

Although PCI procedures can reduce CHD symptoms by dilating the artery and placing a stent, the incidence of in-stent restenosis (ISR) and the resulting repeated revascularization is still high.[2] The underlying mechanism for the development of ISR is mainly responsible for inflammation triggered by endothelial and vascular injury occurring 6 months after PCI, and the development of neointimal atherosclerosis within the stent by late endothelial hyperplasia.[3] The rate of progression of stent atherosclerosis is slow, but organized thrombus may contribute to rapid growth of neointima.[4] The average time from PCI to ISR is 12–24 months for DES, which is prone to early development of atherosclerosis and inevitably carries the risk of late stent thrombosis.[5,6] As thrombosis can occur symptomatically or asymptomatically, in-stent plaque rupture may be the cause of associated thrombotic events and may be a substrate for ISR.[7]

Dual antiplatelet therapy (DAPT) with aspirin combined with a P2Y12 inhibitor is standard drug therapy after coronary stenting.[8] Several studies have shown that routine postoperative use of DAPT does not completely prevent the occurrence of ISR. Some studies tried to decrease DAPT usage duration to reduce the rate of bleeding, it increased the rate of stent thrombosis;[9] and the rate of bleeding events was significantly higher with post-PCI triple therapy. Therefore, even with conventional drug therapy after the procedure, ISR formation may not be completely prevented.[10]

Radix Salviae decoction (RSD), an herbal formula containing a variety of active ingredients,[11] including *Radix Salviae*, sandalwood, and sand kernel, is known for its ability to activate blood circulation, remove blood stasis, and relieve pain.[11] In basic research, the active ingredients of RSD have been shown to have a variety of different mechanisms of action,[12] such as anticoagulation, anti-inflammatory, antioxidant,[13] endothelial cell protection,[14] reduction of mitochondrial depolarization, reduction of pro-apoptosis, and increase of anti-apoptotic proteins,[15] thus reducing ischemia-reperfusion injury, vascular endothelial injury, and thrombosis. In clinical studies, several studies have shown that RSD can improve the symptoms of CHD, angina pectoris, and slow arrhythmias in heart disease.[16] Through its pharmacological mechanism, it can reduce the risk of myocardial ischemia and myocardial infarction,[17] and improve cardiac function and myocardial metabolism, etc.[18] In addition, network pharmacology has been increasingly used to explore potential mechanisms of herbs including *Radix Salviae*.[19–21] Our previous study used network pharmacology to find that a total of 33 bioactive compounds from *Radix Salviae*, including luteolin and Tanshinone IIA, were involved in PI3K-Akt and lipid-atherosclerosis pathways.[21]

Thus, it is of great significance to reduce the incidence of ISR and decrease repeated revascularization after PCI in the clinic, which is still too frequent with conventional DAPT treatment. Fortunately, both clinical and basic studies of RSD have shown that its components have potential therapeutic effects for CHD. Based on the above analysis of ISR formation mechanism and RSD mechanism of action, it is therefore hypothesized that RSD may be effective in preventing ISR formation. However, there was no solid clinical report investigating the efficacy and safety of RSD in preventing ISR occurrence. Thus, this pilot prospective clinical study was designed to investigate the effectiveness of the RSD herbal formula for preventing coronary stenosis and restenosis in the CHD patients after PCI, in order to provide pioneering clinical evidence for further large-scale multicenter studies.

Materials and methods

Ethical approval and informed consent

This study was carried out in accordance with the recommendations of the 2019 Guidelines for Percutaneous Coronary Intervention in China (Chinese Society of Cardiology). The protocol was approved and registered at the Ethics Committee of Guangdong Provincial Hospital of Traditional Chinese Medicine (http://183.62.15.51:9081/GZGCP/index.jsp), with the approval number BF2022-052. All subjects gave written informed consent in accordance with the Declaration of Helsinki. This study is registered at https://www.chictr.org.cn/index.html. The registration identification number is ITMCTR2024000028.

Sample size estimation

According to the literature about the medication effect in preventing ISR occurrence,[22] the rate of the experimental group was 0.0364, while the rate of the control group was 0.2640. The two-tailed alpha was 0.05, beta was 0.2, and the sample size ratio of the two groups was set as 1:1. The sample size was calculated as 43 cases in the experimental group and 43 cases in the control group. A total of 86 cases needed to be enrolled.

Patient source

According to the diagnosis, 86 patients were initially enrolled in the group according to the sample size estimation. After screening by inclusion and exclusion criteria, a preliminary selection was made of 60 patients who underwent PCI surgery diagnosed with CHD with TCM syndrome of *Qi* stagnation and blood stasis, which were included for group allocation. These patients were enrolled at Guangdong Provincial Hospital of Traditional Chinese Medicine between 2020 and December 2021, and were divided into two groups of 30 cases each, a basic medication group for preventing and treating CHD (control group) and RSD Treatment group combined with basic medication (RSD group). The demographic data and underlying diseases (e.g., hypertension, hyperglycemia, hyperlipidemia) were collected as baseline characteristics.

Group treatments

For the control group, basic medication treatment typically includes antiplatelet, lipid-lowering, heart rate control, and controlling high blood pressure or high blood sugar. For the RSD group, RSD granules were taken orally (15 g *Radix Salviae*, 10 g sandalwood, and 10 g sand kernel, decocted in water and taken twice a day for 5 days). Both groups maintained basic medication after discharge.

Diagnostic criteria

The diagnostic criteria for CHD in patients and the standard for PCI followed the 2019 guidelines for PCI in China.

Inclusion and exclusion criteria

Criteria for inclusion were a diagnosis of CHD that met the criteria for PCI, the ability to complete follow-up, and voluntary partici-

Table 1. Comparison of the baseline characteristics of the study groups

Variable	Control, *n* = 28	RSD, *n* = 30	*p*
Basic inflammation			
Sex			0.425
Female	7 (25.0)	4 (13.3)	
Male	21 (75.0)	26 (86.7)	
Age	61.2 (11.9)	61.7 (12.4)	0.888
Days in hospital	10.0 (7.00; 11.2)	7.00 (7.00; 10.0)	0.055
Diagnosis			0.656
Angina	22 (78.6)	21 (70.0)	
MI	6 (21.4)	9 (30.0)	
Comorbidity			
Hypertension	20 (71.4)	16 (53.3)	0.251
DM	10 (35.7)	14 (46.7)	0.562
Hyperlipidemia	14 (50.0)	21 (70.0)	0.198
Comorbidities, *n*			0.663
0	6 (21.4)	3 (10.0)	
1	9 (32.1)	11 (36.7)	
2	8 (28.6)	8 (26.7)	
3	5 (17.9)	8 (26.7)	

Results are *n* (%) or median (interquartile range). DM, diabetes mellitus; MI, myocardial infarction; RSD, *Radix Salviae* decoction.

pation with the signing of an informed consent form. Criteria for exclusion are abnormal mental consciousness, inability to cooperate, or unstable vital signs, relevant drug contraindications or allergies, or participation in other clinical trials within the past month. Patients over 85 years of age, pregnant, or planning to become pregnant, lactating women, or infants were also excluded.

Criteria for abscission

Firstly, patients who withdrew from the trial without experiencing adverse reactions or poor efficacy. Secondly, Patients lost to follow-up.

Criteria for termination

Firstly, the investigators believed that it was medically necessary to terminate the trial for the participants. Secondly, patients could voluntarily withdraw from the trial. Thirdly, those who experienced severe adverse reactions and could not continue treatment.

Patient follow-up and primary and secondary outcomes

Patients were followed up for 1 year after discharge. The primary outcome was the post-PCI restenosis rate. The secondary outcome was the incidence of newly developed stenosis. All outcomes were monitored for about 1 year after the PCI procedure. Restenosis and newly developed stenosis were detected by angiography or coronary computed tomography.

Safety index and monitoring of adverse reactions

We collected safety indicators related to hematology, including aspartate aminotransferase (referred to as AST), alanine aminotransferase (ALT), creatinine (referred to as Cr), and the international normalized ratio (INR) both before and after treatment. We closely monitored patients for adverse reactions during treatment. Any adverse reactions were observed, addressed if necessary, and promptly recorded.

Statistical analysis

Collected data were analyzed with SPSS (v26.0; IBM Corp., Armonk, NY USA) and R (v3.6.2, http://www.r-project.org) software. Continuous data were reported as means ± SD and tested for normal distribution using the Kolmogorov-Smirnov test. If the continuous data followed a normal distribution, Student's *t*-test for independent samples was used for comparison between the two groups. Otherwise, a Mann-Whitney *U* test was used. Categorical variables were reported as frequency and proportion (%) and intergroup comparisons were performed with the chi-square test with or without continuity correction or Fisher's exact test. A p-value < 0.05 was considered statistically significant.

Results

Demographic characteristics of subjects

A total of 60 patients were initially enrolled based on the criteria. Two patients were lost to follow-up and the remaining 58 completed follow-up and were included in the final analysis. No significant differences were observed in demographic characteristics, including sex, age, diagnostic subtype, and comorbidities, between the control group ($n = 28$) and the RSD group ($n = 30$) (Table 1).

Baseline vessel stenosis characteristics before PCI

Before examining the effect of RSD, we compared the baseline

Table 2. Characteristics of stenotic vessels in the study groups

Variable	Control, *n* = 28	RSD, *n* = 30	*p*
Location of stenosis			
LAD			0.266
none	1 (3.57)	3 (10.0)	
proximal	12 (42.9)	9 (30.0)	
middle	13 (46.4)	18 (600)	
distant	2 (7.14)	0 (0.00)	
LCX			0.501
none	6 (21.4)	8 (26.7)	
proximal	7 (25.0)	7 (23.3)	
middle	9 (32.1)	5 (16.7)	
distant	6 (21.4)	10 (33.3)	
RCA			0.221
none	3 (10.7)	3 (10.0)	
proximal	11 (39.3)	5 (16.7)	
middle	10 (35.7)	13 (43.3)	
distant	4 (14.3)	9 (30.0)	
Vessels in stenosis in %			
LAD	90.0 (77.5; 95.0)	85.0 (58.8; 90.0)	0.349
LCX	80.0 (50.0; 90.0)	67.5 (7.50; 98.8)	0.771
RCA	85.0 (63.8; 91.2)	82.5 (52.5; 95.0)	0.969
Total occlusion	17 (60.7)	14 (46.7)	0.419
Stenotic vessels, *n*			0.809
0	1 (3.57)	1 (3.33)	
1	3 (10.7)	3 (10.0)	
2	3 (10.7)	6 (20.0)	
3	21 (75.0)	20 (66.7)	

Results are *n* (%) or median (interquartile range). LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; RSD, *Radix Salviae* decoction.

characteristics of vessel stenosis between the control group and the RSD group prior to PCI. The location of vessel stenosis was divided into proximal, mid, and distal, and no significant differences in stenotic vessel characteristics were observed between the two groups ($p > 0.05$). The degree of stenosis was also calculated as a percentage of occlusion area, and differentiation was made based on whether the occlusion was complete or not. No significant differences were found between the two groups ($p > 0.05$). When comparing the number of vessels in a narrow state before PCI, no statistically significant differences were found ($p > 0.05$) (Table 2).

Characteristics of implanted stent features during PCI

The characteristics of stents implanted during PCI were compared as they could affect the prognosis of future restenosis. No significant statistical differences were found between the two groups ($p > 0.05$) in stent diameter, length, or the number of stents implanted during PCI (Table 3). These results suggest that the baseline characteristics of the control group and RSD group in terms of vascular stenosis and stent characteristics implanted during PCI were similar, and when combined with the demographic characteristics of the subjects, indicate that the baseline of these two groups was comparable.

Effects of RSD on restenosis in culprit vessels after PCI

Restenosis severity was assessed by dividing the degree of stenosis into less than or more than 50% of the arterial lumen area, and calculating the number of restenosis cases for each vessel. The left circumflex artery (LCX) had the lowest severity of restenosis. Statistical analysis revealed no significant difference in restenosis percentage between the control group and the RSD group for all three arteries ($p > 0.05$). Further statistical analysis of restenosis types for each vessel also showed similar results, with no significant difference found between the two groups for any individual artery ($p > 0.05$). A comparison of the number of restenotic vessels did not show statistical significance ($p > 0.05$) (Table 4). These data suggest that RSD did not show any significant effect on im-

Table 3. Characteristics of stents placed in stenotic vessels in the study groups

Variable	Control, *n* = 28	RSD, *n* = 30	*p*
Stent diameter in mm			
LAD	1.31 (0.00; 3.00)	0.00 (0.00; 2.87)	0.794
LCX	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)	0.708
RCA	0.00 (0.00; 3.31)	0.00 (0.00; 2.72)	0.246
Stent length in mm			
LAD	9.00 (0.00; 32.6)	0.00 (0.00; 23.8)	0.264
LCX	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)	0.575
RCA	0.00 (0.00; 28.0)	0.00 (0.00; 29.5)	0.750
Stents, *n*			0.684
1	15 (53.6)	18 (60.0)	
2	12 (42.9)	10 (33.3)	
3	1 (3.57)	2 (6.67)	

Results are *n* (%) or median (interquartile range). LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; RSD, *Radix Salviae* decoction.

proving post-PCI restenosis.

Effects of RSD on neostenosis in nonculprit vessels after PCI

As RSD did not significantly affect restenosis, we investigated the impact of RSD on newly developed stenosis after PCI, which we refer to as new stenosis. We compared this with the baseline and post-PCI stenosis of the blood vessels. The results showed that there was no significant difference in the percentage of new stenosis between the control group and the RSD group in these three arteries ($p > 0.05$). We also calculated the number of nonprimary vessel stenoses that increased after PCI, and found no significant difference between the control group and the RSD group ($p > 0.05$) (Table 5). These data suggest that RSD therapy did not reduce the incidence of new stenosis in nonprimary vessels following PCI.

Table 4. Characteristics of vessels in restenosis after PCI in the study groups

Variable	Control, *n* = 28	RSD, *n* = 30	*p*
Restenosis, %			
LAD	0.00 (0.00 ;0.00)	0.00 (0.00; 0.00)	0.301
LCX	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)	-
RCA	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)	0.122
Vessels in restenosis, *n*			0.707
0	26 (92.9)	25 (83.3)	
1	2 (7.14)	5 (16.7)	
Restenosis type			
LAD			0.483
0	27 (96.4)	30 (100)	
3	1 (3.57)	0 (0.00)	
LCX			–
0	28 (100)	30 (100)	
RCA			0.096
0	27 (96.4)	25 (83.3)	
1	0 (0.00)	4 (13.3)	
2	0 (0.00)	1 (3.33)	
4	1 (3.57)	0 (0.00)	

Results are *n* (%) or median (interquartile range). LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; PCI, percutaneous coronary intervention; RCA, right coronary artery; RSD, *Radix Salviae* decoction.

Table 5. Comparison of the number of vessels in neostenosis after PCI in the study groups

Variable	Control, *n* = 28	RSD, *n* = 30	*p*
Neostenosis, %			
LAD	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)	0.446
LCX	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)	0.676
RCA	0.00 (0.00; 0.00)	0.00 (0.00; 7.50)	0.469
Vessels in neostenosis, *n*			0.400
0	17 (60.7)	13 (43.3)	
1	8 (28.6)	11 (36.7)	
2	3 (10.7)	6 (20.0)	

Results are *n* (%) or median (interquartile range). LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; PCI, percutaneous coronary intervention; RCA, right coronary artery; RSD, *Radix Salviae* decoction.

Multifactor logistic regression analysis for ISR or neostenosis incidence

As differences of the RSD treatment-associated reduction in ISR or neostenosis incidence after PCI were not significant, we analyzed the factors that may have affected the occurrence of ISR or neostenosis. Although multifactor logistic regression analysis of the ISR incidence did not find any significantly associated factors (Table 6), the diagnosis of MI/angina (p = 0.031), average stent length (p = 0.010) and ALT (p = 0.027) were found to be significantly associated with neostenosis occurrence (Table 7).

Between-group comparison of common clinical indicators

To evaluate the efficacy of treatment to common clinical indicators that were closely related to CHD and ISR occurrence, we compared the indicators before and after treatment in the two groups, including body weight, systolic/diastolic blood pressure (SBP/DBP), low-density lipoprotein (LDL)-cholesterol, and hemoglobin A1c (HbA1c). The results showed there were no significant changes in these indicators in the two groups either before or after treatment ($p > 0.05$) (Table 8).

Safety index in hematology

To assess the safety of renal sympathetic denervation for the treatment of coronary artery stenosis and restenosis, we measured hematological parameters such as AST, ALT, Cr, and INR to evaluate liver and kidney function and coagulation. Comparison of these hematological parameters before and after treatment did not reveal any significant differences between the control group and the RSD group ($p > 0.05$) (Table 9), indicating that RSD had a good safety profile in clinical treatment.

Adverse reactions

In clinical treatment, there were no observed adverse reactions or serious adverse reactions associated with RSD in either the control group or the RSD group. Together with the hematological

Table 6. Multifactor logistic regression analysis of ISR occurrence

Variable	B	SE	Wals	*p*	Exp (B)
Sex	−478.535	34,037.470	0.000	0.989	0.000
Age	13.437	947.063	0.000	0.989	6.850E+5
Days in hospital	−5.477	5,584.037	0.000	0.999	0.004
MI/angina	121.665	100,330.728	0.000	0.999	6.893E+52
Hypertension	−39.138	5,474.732	0.000	0.994	0.000
DM	81.574	85,987.229	0.000	0.999	2.673E+35
Hyperlipidemia	−14.845	125,004.392	0.000	1.000	0.000
AST	0.852	355.185	0.000	0.998	2.343
ALT	0.043	742.722	0.000	1.000	1.044
Cr	−3.551	2,408.717	0.000	0.999	0.029
INR	−643.202	33,927.690	0.000	0.985	0.000
Vessels in stenosis, #	−25.3	24,559.627	0.000	0.999	0.000
Average stent diameter	−41.076	27,394.159	0.000	0.999	0.000
Average stent length	−53.152	1,960.253	0.001	0.978	0.000
Stent, #	264.242	11,905.468	0.000	0.982	5.736E+114

ALT, alanine transaminase; AST, alanine transaminase; Cr, creatinine; DM, diabetes mellitus; INR, international normalized ratio; ISR, in-stent stenosis; MI, myocardial infarction.

Table 7. Multifactor logistic regression analysis of neostenosis occurrence

Variable	B	SE	Wals	*p*	Exp (B)
Sex	0.255	0.992	0.066	0.797	1.290
Age	0.054	0.039	1.839	0.175	1.055
Days in hospital	−0.007	0.100	0.005	0.941	0.993
MI/angina	4.021	1.864	4.652	0.031*	55.760
Hypertension	−0.257	0.837	0.094	0.759	0.773
DM	−0.921	0.952	0.936	0.333	0.398
Hyperlipidemia	0.407	0.900	0.205	0.651	1.503
AST	0.006	0.010	0.339	0.561	1.006
ALT	0.071	0.032	4.866	0.027*	1.073
Cr	0.007	0.012	0.402	0.526	1.007
INR	0.379	2.069	0.034	0.855	1.461
Stenotic vessels, *n*	0.323	0.544	0.353	0.552	1.381
Average stent diameter	−1.965	1.949	1.016	0.313	0.140
Average stent length	0.528	0.205	6.653	0.010*	1.695
Stent, #	−0.380	0.771	0.243	0.622	0.684

*$p < 0.05$. ALT, alanine transaminase; AST, alanine transaminase; Cr, creatinine; DM, diabetes mellitus; INR, international normalized ratio; MI, myocardial infarction.

indicators, these results indicate that RSD was safe for the treatment of CHD.

Discussion

This clinical study aimed to investigate the impact of RSD on coronary stenosis and restenosis, however, our data did not show significant benefits of RSD in preventing the occurrence of restenosis and neostenosis. Many factors can promote the formation of ISR, such as inflammatory state, platelet aggregation, vessel wall damage, thrombosis, and increased cholesterol absorption.[22] Stent placement and the number and type of stents implanted can cause mechanical damage.[23] Loss or abnormality of endothelial functional integrity can stimulate an inflammatory response in the

Table 8. Comparison of the clinical indicators common to the study groups

Variable	Control, *n* = 28	RSD, *n* = 30	*p*
Weight in kg			
Before treatment	68.9 (14.8)	71.0 (10.3)	0.580
After treatment	68.5 (13.4)	70.4 (12.6)	0.605
SBP in mmHg			
Before treatment	137 (18.4)	129 (15.3)	0.090
After treatment	135 (19.9)	131 (17.1)	0.463
DBP in mmHg			
Before treatment	79.0 (75.5; 90.5)	75.5 (72.2; 80.0)	0.087
After treatment	79.0 (71.5; 91.5)	80.0 (73.5; 84.8)	0.801
LDL in mmol/L			
Before treatment	2.98 (1.07)	2.91 (1.14)	0.821
After treatment	1.93 (1.66; 2.17)	1.98 (1.42; 2.39)	0.892
HbA1c, %			
Before treatment	6.10 (5.90; 7.60)	6.20 (5.73; 6.80)	0.248
After treatment	6.20 (5.93; 7.30)	6.00 (5.90; 6.90)	0.477

Results are *n* (%) or median (interquartile range). DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; RSD, *Radix Salviae* decoction; SBP, systolic blood pressure.

Table 9. Comparison of the hematological indicators in the study groups

Variable	Control, *n* = 28	RSD, *n* = 30	*p*
Before treatment			
AST	19.9 (16.8; 27.3)	24.6 (18.2; 42.7)	0.075
ALT	16.9 (12.8; 27.2)	27.5 (16.3; 45.1)	0.083
Cr	77.2 (72.2; 90.7)	81.2 (66.0; 95.4)	0.791
INR	0.98 (0.95; 1.03)	0.94 (0.90; 1.00)	0.117
After treatment			
AST	17.2 (15.2; 25.9)	20.0 (15.7; 23.4)	0.570
ALT	19.7 (13.3; 31.0)	20.5 (13.9; 32.6)	0.779
Cr	79.5 (73.9; 93.1)	81.3 (72.2; 93.0)	0.870
INR	0.92 (0.91; 0.95)	0.94 (0.90; 0.97)	0.737

ALT, alanine transaminase; AST, alanine transaminase; Cr, creatinine; INR, international normalized ratio.

artery, causing intimal hyperplasia, stenosis, and sclerosis. Drug treatment to prevent restenosis is a common intervention after percutaneous stenting procedures. These medications include antiplatelet agents,[24] anticoagulants, anti-inflammatory,[25] and antioxidants. However, the continuation of conventional drug therapy after PCI for CHD still cannot completely prevent the formation of ISR for several possible reasons. First, there is a wide variation in the body composition of different individuals who are resistant to conventional drugs,[24] and the increase in drug resistance may increase the risk of thrombotic complications after PCI.[26] Secondly, patient lifestyle (e.g., smoking) and medication compliance,[27] as well as disease comorbidities (e.g., hypertension, diabetes, anemia,[28] etc.) may increase the possibility of ISR formation. In addition, stent type, low stent implantation pressure, and multiple stent placement are strongly associated with ISR in patients after PCI.[29] One study found that longer stent length and smaller stent diameter are likely it is to increase the incidence of ISR 8–12 months after PCI.[29]

Studies have shown that RSD is an important prescription for the treatment of cardiovascular diseases. The main mechanisms of action include anticoagulation, anti-inflammation, antioxidation, protection of endothelial cells, reduction of mitochondrial depolarization, reduction of pro-apoptosis and increase of anti-apoptotic proteins, which protect blood vessels, reduce thrombosis, prevent myocardial hypoxia-induced injury and myocardial infarction. Many studies have confirmed that RSD interferes with signaling pathways related to atherosclerosis through various pathways to achieve therapeutic effects.[30,31] A network pharmacology analysis showed that RSD has 67 potential active ingredients and 109 therapeutic targets in the treatment of ischemic cardiomyopathy (ICM).[21] Another network pharmacology and experimental analysis suggested that RSD had antiatherosclerotic and endothelial-to-mesenchymal transition activity via the LASP1/PI3K/AKT pathway, providing a possible therapeutic intervention for atherosclerosis.[30] RSD mediated therapeutic effects by modulating atherosclerosis-related biological processes and signaling pathways.[31] In addition, the monarch *Salviae* protects the heart from ischemia and reperfusion injury.[32] For example, Tanshinone IIA,[33] the main lipid-soluble component of *Radix Salviae*,[34] has anti-inflammatory and antioxidant activities. Both the ethanolic extract of *Salviae* and the aqueous extract of *Salviae* have blood nourishing and tonic properties. Some clinical studies have also shown that RSD improved the symptoms of CHD, angina pectoris, and slow arrhythmias in cardiac disease. Through its pharmacological mechanism, it reduces the risk of myocardial ischemia and myocardial infarction, and improves cardiac function and myocardial metabolism, etc. RSD is also widely used in the treatment of hypertension, hyperlipidemia, and other diseases.[35] The underlying mechanism of ISR development is inflammation triggered by endothelial and vascular injury occurring 6 months after PCI and the appearance of atherosclerosis within the stent in late endothelial hyperplasia. Based on the mechanism of action of RSD and the underlying mechanism of ISR formation, as well as previous relevant basic and clinical studies, we suggest that RSD may prevent the formation of ISR.

Normally, conventional secondary preventive therapy drugs for CHD including DAPT are used to prevent ISR. For the treatment of ISR, the most used intervention is PCI, including cutting balloons, drug-eluting balloons, DES, and excimer laser coronary atherectomy. Some pioneering studies on the preventive medication to ISR showed that thiazolidinedione (TZD) treatment for 6 to 18 months significantly reduced the incidence of ISR, target lesion revascularization, and major adverse cardiovascular events in patients after PCI, and Pioglitazone treatment seems to have more beneficial effects than Rosiglitazone.[36] Nevertheless, few studies have shown the efficacy and safety of herbal medicines in preventing ISR incidence. Our data in another study found that RSD combined with remote ischemic preconditioning did not significantly affect angina attack and prognosis of CHD, but decreased the frequency of emergency medications in CHD patients, indicating a therapeutic effect of RSD in CHD. Herein, our data in this study also partially indicate a therapeutic trend of RSD in preventing ISR incidence, although we did not observe the statistical significance. This pilot study will help to design further studies in investigating RSD effects to stenosis in the future.

Multifactor logistic regression analysis was used to further screen the factors that might affect ISR or neostenosis incidence. Although multifactor logistic regression analysis for the ISR incidence did not find significantly associated factors, the diagnosis of MI/angina, average stent length, and ALT level was found to be significantly associated with neostenosis occurrence. These data were consistent with previous reports that the patient, stent, and lesion-related predictors were particularly important for predicting stenosis after PCI.[37–39]

Limitations

The results observed in this pilot study have some limitations.

Firstly, the sample size was relatively small, the number of finally enrolled subjects was limited, and it was influenced by individual differences. There is a possibility of sampling bias compared with the overall population, and the trial design needs to be improved. Secondly, the duration of RSD administration in the test group of this study was relatively short. Further study with a longer dosing time is planned to investigate and confirm the clinical efficacy of RSD for ISR prevention. Thirdly, the integrated target effects of the active ingredients of RSD may be different for systemic and local effects, which needs to be improved by researchers in basic experiments and clinical trials.

Future perspectives

The negative result in ISR occurrence in this study may have been associated with the relatively small sample size and short duration of RSD administration. Studies with more patients and prolonged RSD duration will be performed to investigate the RSD effects in regulating stenosis after PCI.

Conclusions

This study was designed to test the additional efficacy of RSD plus conventional treatment for coronary artery restenosis and neostenosis, compared with the conventional treatment given to the control group. Our data showed that although the addition of RSD for a short period did not significantly change restenosis and neostenosis occurrence after PCI, the diagnosis of MI/angina, average stent length, and ALT levels were significantly associated with neostenosis occurrence. This pilot study will provide preliminary evidence for designing further studies to investigate RSD effects to stenosis in the future.

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Conflict of interest

The authors declared that there is no conflict of interests in the authorship and publication of this contribution.

Author contributions

Designed the study and finalized the manuscript (QL), collected patient information and constructed the dataset (PZL, PCD, QQL), completed the first version of the manuscript (RYY, QL), finished the manuscript corrections (QL, DWW), and finished the manuscript revisions (QL, AMZ). All authors read and approved the final manuscript

Ethical statement

This study was carried out in accordance with the recommendations of the 2019 Guidelines for Percutaneous Coronary Intervention in China (Chinese Society of Cardiology). The protocol was approved and registered at the Ethics Committee of Guangdong Provincial Hospital of Traditional Chinese Medicine (http://183.62.15.51:9081/GZGCP/index.jsp), with the approval registration number BF2022-052. All subjects gave written informed consent in accordance with the Declaration of Helsinki. This study is registered at https://www.chictr.org.cn/index.html. The registration identification number is ITMCTR2024000028.

Data sharing statement

No additional data are available.

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