Protective effects of salvianolate on myocardial injury or myocardial infarction after elective percutaneous coronary intervention in NSTE-ACS patients: a randomized placebo-controlled trial

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Research article

Keywords: Myocardial infarction; Acute coronary syndrome; Percutaneous coronary intervention; Salvianolate

Posted Date: November 17th, 2019

DOI: https://doi.org/10.21203/rs.2.17237/v1

Version of Record: A version of this preprint was published at Chinese Journal of Integrative Medicine on June 22nd, 2020. See the published version at https://doi.org/10.1007/s11655-020-2728-0.

Abstract

Percutaneous coronary intervention (PCI) can cause myocardial injury or myocardial infarction. There is unmet need to reduce incidence or severity of PCI related myocardial injury or myocardial infarction. This study is to evaluate the protective effects of salvianolate on PCI related myocardial injury or myocardial infarction after elective PCI in non-ST-segment elevation acute coronary syndrome (NSTE-ACS) patients. Methods We enrolled patients with NSTE-ACS who underwent elective PCI. The patients were randomly assigned to the salvianolate group or the control group. The incidence and the severity of PCI related myocardial injury or myocardial infarction, in addition to major adverse cardiac events (MACEs) during one year follow-up after PCI were studied between the two groups. We also performed a multivariate logistic regression analysis to determine the independent factors for PCI related myocardial injury or myocardial infarction after elective PCI. Results Compared with the control group, salvianolate treatment reduced the incidence of PCI related severe myocardial injury or myocardial infarction (11.7% vs 26.5%, p = 0.035). The rate of MACEs or all-cause death within one month or one year after the procedure was not significantly different between the two groups. Conclusions Periprocedural treatment with salvianolate reduces the incidence of PCI related severe myocardial injury or myocardial infarction, although it does not influence clinical prognosis.

Background

Percutaneous coronary intervention (PCI) plays a major role in reducing coronary artery stenosis and alleviate ischemic symptoms. However, PCI related myocardial injury or myocardial infarction occurs approximately 20-40% in stable coronary artery disease (CAD) and 40-50% in myocardial infarction patients who received elective PCI [1]. Zeitouni has reported that PCI related myocardial infarction could negatively impact on clinical prognosis [2]. It is challenging to reduce incidence or severity of PCI related myocardial injury or myocardial infarction. It has significant benefit to find any therapy to alleviate PCI related myocardial injury or myocardial infarction, finally to improve clinical prognosis. Salvianolate is a traditional Chinese medicine extracted from salvia. Previous studies have confirmed that salvianolate has multiple effects including anti-inflammation [3], anti-platelet [4] and coronary microcirculation improvement [5], which could be a good candidate to improve PCI related myocardial injury or myocardial infarction. Till now, there has been no clinical data about whether salvianolate can reduce incidence or severity of PCI-related myocardial injury or myocardial infarction in non-ST-segment elevation acute coronary syndrome (NSTE-ACS) patients undergoing elective PCI. We designed this randomized placebo-controlled trial to investigate its clinical effects on PCI related myocardial injury or myocardial infarction.

Methods

Patients

All NSTE-ACS patients aged between 18 and 90 years from October 2016 to June 2017 admitted to Huashan Hospital (Shanghai, China) were screened for this study. All patients enrolled have received

elective PCI and had normal cardiac troponin T (cTnT) or elevated cTnT with stable or declining tendency prior to PCI. Written informed consent for PCI and this clinical study was obtained by all participants. Exclusion criteria were the followings: (1) increased pre-PCI cTnT values (rising above 20% of the previous value) or undetermined tendency; (2) severe liver dysfunction (ALT/AST >3 times of normal value, but only AST elevation is not excluded); (3) severe renal dysfunction (creatinine clearance rate <30 ml/min); (4) no informed consent; (5) patients with coronary artery bypass grafting history.

Study design

Eligible patients were randomized as the salvianolate group or the control group via simple random classification. Patients in the salvianolate group received intravenous salvianolate solution 200mg/100ml 2h before PCI, 22h and 46h after PCI with a rate of 60 ml/h. Patients in the control group received intravenous saline with the same volume and rate. All enrolled patients received standard medical care in accordance with the guidelines for the management of patients with NSTE-ACS, such as anti-platelet, anticoagulation therapy, lipid-lowering therapy, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), or other antihypertensive therapy if clinically indicated. PCI was performed according to the current guidelines for the management of acute coronary syndromes [6]. The specific intervention strategies were dependent on cardiologists' discretion. All patients were followed up in outpatient service or telephone interview at one month and one year after PCI. Our study adheres to CONSORT guidelines.

Study definition

PCI related myocardial injury or myocardial infarction was diagnosed according to the third universal definition of myocardial infarction [7]. PCI related myocardial infarction (PMI) meets the criteria including: (1) cTnT values >5 times of upper reference limit (URL) after PCI if patients with normal baseline cTnT values; (2) post-PCI cTnT values rising >20% of pre-PCI value if patients with elevated pre-PCI cTnT values but cTnT levels are stable or falling. In addition, at least one of the following criteria must be present: (1) evidence of prolonged ischemia (>20 min) as demonstrated by prolonged chest pain; (2) ischemic ST changes or new pathological Q waves; (3) angiographic evidence of a flow limiting complication including loss of patency of a side branch, persistent slow-flow, no-reflow, or embolization; (4) imaging evidence with lack of viable myocardium or new regional wall motion abnormality. For patients who have isolated cTnT elevation after PCI, they can only be diagnosed as PCI related myocardial injury.

We further categorized all PCI-related myocardial injury into mild myocardial injury or severe myocardial injury. Mild myocardial injury was defined as increase of post-PCI cTnT values <5 times URL with normal baseline values or a rise of post-PCI cTnT values <20% of the baseline value with elevated pre-PCI cTnT; Severe myocardial injury was an elevation of cTnT values >5 times with normal baseline values or a rise

of post-PCI cTnT values >20% of the baseline value with elevated pre-PCI cTnT in the absence of ischemic, angiographic or imaging findings. Major coronary artery with stenosis more than 50% is defined as impaired vessel.

Measurements

Blood samples were collected in all enrolled patients before and at 8, 24 and 48h after PCI to measure cTnT to diagnose PCI related myocardial injury or myocardial infarction. Other baseline biochemical markers were also obtained.

Baseline characteristics including age, body mass index (BMI), past medical history were collected. Angiographic features and procedural characteristics were recorded. Data of patients were collected under anonymous conditions at Huashan Hospital.

Study endpoints

The primary endpoint of this study is the incidence of severe myocardial injury or myocardial infarction after PCI. Secondary endpoints are all-cause death and incidence of major adverse cardiac events (MACEs), such as cardiovascular death, hospitalization for heart failure, myocardial infarction, stent thrombosis, or target vessel revascularization within one year after PCI.

Statistical Analysis

Data from all participants were analyzed based on per-protocol (PP) analysis. Baseline clinical and demographic characteristics in addition to angiographic and intervention features were expressed as mean ± SD or median according to their distribution. Normally distributed values were compared by Student t-test. Otherwise, Mann–Whitney U test was used. The differences of proportions were analyzed using the Chi-square test. Multivariate logistic regression was used to find independent protective factors for PCI related severe myocardial injury or myocardial infarction. The difference of prognosis between control group and salvianolate group was analyzed using Logrank test. Two-sided tests were used and values of $p < 0.05$ were considered to be significant. All analysis was conducted using SAS 9.4 software (SAS institute Inc., Cary, USA).

Results

Patient enrollment

There are 242 patients were screened from October 2016 to June 2017. Among them, 43 patients were excluded because of emergent PCI, 21 patients were excluded for pre-procedural abnormal cTnT with undetermined trend, 23 patients were excluded due to severe hepatic or renal dysfunction, and 6 patients were excluded due to lack of informed consent (Figure 1). There were total 149 patients qualified initially and salvianolate or saline was given during procedure. After coronary angiography (CAG), 21 patients were excluded since no PCI received. Finally 128 patients were enrolled with PCI therapy.

Patient characteristics

Demographic and clinical features of patients in control group and salvianolate group are shown in Table 1, with no statistically different between the two groups.

Coronary angiography and PCI characteristics

There was no significant finding in the number of impaired coronary artery vessels or target vessels pre-PCI TIMI flow grade between control group and salvianolate group. Similar results are found regarding number of coronary artery or segments received PCI, number of stents implanted, total stent length, or target vessels post-PCI TIMI flow grade (Table 2).

Primary end point

The univariate analysis showed that salvianolate treatment resulted in less severe myocardial injury or myocardial infarction after PCI compared with the control group (11.7% vs 26.5%, $p = 0.035$) in Table 3. Multivariate analysis with different models all confirmed salvianolate treatment resulted in less severe myocardial injury or myocardial infarction (Table 4).

Secondary end points

There was no significant difference about incidence of all-cause death and MACEs at one month and one year after PCI between control group and salvianolate group (Table 5 and 6). Kaplan-Meier survival curves of one-year without MACEs between two groups showed no significant difference (Figure 2).

Drug safety

Salvianolate intravenous injection was safe in clinical application and no adverse reaction was observed during periprocedural period in our study.

Discussion

As a randomized placebo-controlled clinical study, we reported for the first time that salvianolate treatment during periprocedural period could reduce the severity of PCI related myocardial injury or myocardial infarction in NSTE-ACS patients. NSTE-ACS represents the most frequent indication for CAG and PCI worldwide. According to clinical manifestations and GRACE score, many NSTE-ACS patients can receive elective PCI with stable or declining cTnT pre-PCI [6]. Elective PCI with stable or declining cTnT pre-PCI allows us to investigate incidence and severity of PCI related myocardial injury or myocardial infarction as any new increase of cTnT after PCI reflects the damage from the procedure. Between control group and salvianolate group, there is no significant difference in baseline characteristics, therefore no noticeable selection bias in this study. For the primary end point, salvianolate treatment reduced severe myocardial injury or myocardial infarction. After adjustment for many confounding factors, salvianolate treatment still showed significant benefits after PCI, which confirmed salvianolate treatment is a strong and independent factor to improve PCI related myocardial injury or myocardial infarction.

PCI related myocardial injury or myocardial infarction is crucial to influence clinical prognosis [2]. In a previous observational study, patients with periprocedural myocardial injury and myocardial infarction have a higher rate of cardiovascular events at thirty days and at one year after PCI [2]. The pathogenesis of PCI related myocardial injury or myocardial infarction includes vulnerable plaque disruption, distal embolization [8,9], ischemia/reperfusion injury, oxidative stress, platelet activation [10], inflammatory cytokines activation [11] or endothelial cell injury induced by balloon inflation or stent implantation during the procedure. When vascular endothelial cells are significantly injured, vasoconstricting factors and cell chemokines are released followed by collagen tissue exposed [11], which leads to platelet activation, aggregation and adhesion. Finally thrombosis is formed which causes myocardial damage. These mechanisms may interact with each other, which can aggravate the final outcome [13].

Salvianolate is extracted from Salvia miltiorrhiza which contains magnesium lithospermate B, rosmarinic acid and lithospermic acid [14-16]. Salvianolate treatment showed less severe myocardial injury or myocardial infarction after PCI via its diverse pharmacological effects. Previous study showed that salvianolate inhibited human platelet activation via phosphodiesterase (PDE) or antagonizing P2Y12 receptor [4]. Salvianolate can also inhibit reactive oxygen species (ROS) production [17] and improve microvascular flow by inhibiting oxidative stress and apoptosis [5]. In addition, salvianolate can reduce serum IL-6, CRP levels or myocardial ischemia reperfusion injury induced by PCI in atherosclerosis rats [3,18].

Salvianolate treatment was safe and well tolerated among multiple clinical studies, including this study. Possible side effects, including headache, dizziness or gastrointestinal reaction, were not different between salvianolate group and control group according to previous studies [19].

However, our study did not find significant difference in prognosis after salvianolate treatment during one year follow-up. The degree of myocardial protection by salvianolate might be not clinically potent enough to impact on clinical prognosis. Larger sample size and multi-center study is warranted to confirm the benefits of salvianolate. We tested salvianolate with 200mg daily for total three days in our study. In a previous study, seven days of salvianolate infusion with 400mg daily can protect contrast-induced nephropathy after PCI [15]. Another study with 400mg daily for 7 days can attenuate microvascular dysfunction after cardiac ischemia and reperfusion which showed smaller infarct size and improved left ventricular systolic function[5]. With salvianolate treatment with 200mg daily for 14 days, it can improve unstable angina pectoris with no significant difference of MACEs [20]. Longer course of treatment or higher dose of treatment can be a future direction.

Conclusion

Our study reports for the first time that salvianolate treatment can alleviate PCI related severe myocardial injury or myocardial infarction. It shines new approach to improve PCI related myocardial injury or myocardial infarction, although salvianolate treatment does not improve clinical prognosis.

Abbreviations

PCI: Percutaneous coronary intervention; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; MACEs: major adverse cardiac events; CAD: coronary artery disease; cTnT: cardiac troponin T; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; PMI:PCI related myocardial infarction; URL: upper reference limit; BMI: body mass index; PP: per-protocol; CAG: coronary angiography; PDE: phosphodiesterase ; ROS: reactive oxygen species

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Huashan Hospital (Shanghai, China) and written informed consent was obtained from each participant prior to study participation. All the data obtained was anonymized. Consent including publishing personal or clinical data from study participants can be requested from Ethics Committee of the Huashan Hospital.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request..

Competing interests

The authors report no conflict of interest.

Author Contributions

WS, XPL, WHF, ZDZ and HMS contributed to the design of the study. YO, SJS, WS and HMS performed the study and collected experiment data. JFL performed the statistical analysis. YZS, YFC and XJL obtained funding for the study. All authors contributed to data analysis and draft of the manuscript.

Funding

This work was financially supported by grants (81673701 and 81573710) from National Natural Science Foundation of China. The funding body had the role in the design of the study, collection, analysis, and interpretation of data, writing the manuscript and decision to publish the findings.

Acknowledgements

Not applicable.

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Tables

Table 1 Demographic and clinical characteristics

Characteristics	Salvianolate group (*n* = 60)	Control group (*n* = 68)	*p* value
Age, year	64.8±11.0	65.2±107	0.803
Male	54 (73.0)	55 (69.6)	0.647
Body Mass Index, kg/m^2	24.9±3.2	24.8±3.4	0.803
Diabetes mellitus	28 (37.8)	24 (30.4)	0.330
Hypertension	42 (56.8)	55 (69.6)	0.099
Systolic blood pressure, mmHg	135.1±18.9	132.0±17.7	0.301
Previous myocardial infarction	8 (10.8)	6 (7.6)	0.491
Previous coronary intervention	9 (12.2)	15 (19)	0.246
Current smoker	30 (40.5)	29 (36.7)	0.627
Normal pre-PCI cTnT	50 (67.6)	64 (81.0)	0.103
Pre-PCI hs-CRP, mg/L	2.6±3.1	3.1±4.3	0.327
Pre-PCI NT-proBNP, pg/mL	498.4±709.4	528.6±883.8	0.854
Pre-PCI serum creatine, μmol/L	73.8±22.0	93±121.2	0.052

Categorical variables are shown as *n* (%), and continuous variables are shown as mean ± standard deviation.PCI, percutaneous coronary intervention; cTnT, cardiac troponin T; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro-B-type natriuretic peptide

Table 2 Coronary angiography and PCI characteristics

Characteristics	Salvianolate group (n = 60)	Control group (n = 68)	p value
Impaired coronary artery vessels			
1	33 (55.0)	37 (54.4)	0.835
2	20 (33.3)	25 (36.8)	
≥3	7 (11.7)	8 (8.8)	
LAD stenosis	34 (56.7)	42 (61.8)	0.558
LCX stenosis	18 (30.0)	17 (25.0)	0.527
RCA stenosis	18 (30.0)	21 (30.9)	0.914
Coronary artery vessels with PCI			0.682
1	41 (68.3)	42 (61.8)	
2	16 (26.7)	23 (33.8)	
≥3	3 (5.0)	3 (20.3)	
Coronary artery segments with PCI			0.849
1	34 (56.7)	37 (54.4)	
2	14 (23.3)	16 (23.5)	
3	11 (18.3)	12 (17.6)	
4	1 (1.7)	3 (4.4)	
Stents implanted			0.936
0	1 (1.7)	4 (5.9)	
1	35 (58.3)	36 (54.5)	
2	14 (23.3)	14 (21.2)	
3	9 (15.0)	12 (18.2)	
4	1 (1.7)	2 (3.0)	

Max of stent diameters, mm	3.0±0.4	3.0±0.4	0.483
Total stent length, mm	40.9±27.3	35.8±25.1	0.735
Bifurcation stent	13 (21.7)	13 (19.1)	0.721
Pre-dilation pressure, atm	12.4±2.7	13.0±3.1	0.244
Stent release pressure, atm	13.4±1.9	13.4±2.0	0.817
Post-dilation pressure, atm	17.0±2.3	17.8±2.3	0.881
Drug coated balloon	1 (1.7)	4 (5.9)	0.370
Target vessel TIMI flow grade before PCI			0.214
0	9 (15.0)	4 (5.9)	
I	0 (0)	2 (2.9)	
II	5 (8.3)	6 (8.8)	
III	46 (76.7)	56 (82.4)	
Target vessel TIMI flow grade after PCI			0.498
0	0 (0)	0 (0)	
I	0 (0)	0 (0)	
II	0 (0)	2 (2.9)	
III	60 (100)	66 (97.1)	

Categorical variables are shown as *n* (%), and continuous variables are shown as mean ± standard deviation.

LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction

Table 3 Primary end point with univariate analysis

Classification	Salvianolate group (*n* = 60)	Control group (*n* = 68)	*p* value
No or mild myocardial injury	53 (88.3)	50 (73.5)	0.035
Severe myocardial injury or myocardial infarction	7 (11.7)	18 (26.5)	

Categorical variables are shown as *n* (%).

Table 4 Primary end point with multivariate analysis

Models	Factor	OR value (95% CI)	*p* value
Model 1	group (1- Salvianolate, 0-control)	0.367 (0.141, 0.953)	0.040
Model 2	group (1- Salvianolate, 0-control)	0.318 (0.115, 0.874)	0.026
	diabetes (1-yes, 0-no)	1.162 (0.423, 3.194)	0.771
	hypertension (1-yes, 0-no)	1.005 (0.344, 2.934)	0.993
	body mass index >28 (1-yes, 0-no)	0.959 (0.843, 1.091)	0.523
	systolic blood pressure (1-yes, 0-no)	0.981 (0.956, 1.006)	0.130
Model 3	group (1- salvianolate, 0-control)	0.337 (0.114, 0.990)	0.048
	diabetes (1-yes, 0-no)	1.056 (0.353, 3.154)	0.923
	hypertension (1-yes, 0-no)	0.966 (0.307, 3.042)	0.953
	body mass index >28 (1-yes, 0-no)	0.943 (0.815, 1.092)	0.432
	systolic blood pressure (1-yes, 0-no)	0.982 (0.957, 1.008)	0.172
	number of stents (1-yes, 0-no)	2.273 (1.083, 4.784)	0.030
	number of main vascular lesions (1-yes, 0-no)	0.961 (0.344, 2.681)	0.939

Data are expressed as odds ratios (95% confidence intervals). All variables are identified as predictors for PCI related myocardial injury or myocardial infarction.

Table 5 Secondary end points at 30 days after PCI

Secondary end points	Salvianolate group (*n* = 60)	Control group (*n* = 68)	*p* value
Major adverse cardiovascular events	3 (5.0)	5 (7.4)	0.722
Hospitalization for heart failure	0 (0)	0 (0)	
Myocardial infarction	3 (5.0)	5 (7.4)	0.722
PMI	3 (5.0)	5 (7.4)	0.722
Stent thrombosis	1 (1.7)	0 (0)	
Target vessel revascularization	0 (0)	0 (0)	
Cardiovascular death	1 (1.7)	0 (0)	
All-cause death	1 (1.7)	1 (1.5)	0.930

Categorical variables are shown as *n* (%).

PMI, PCI related myocardial infarction

Table 6 Secondary end points at one year after PCI

Secondary end points	Salvianolate group (*n* = 60)	Control group (*n* = 68)	*p* value
Major adverse cardiovascular events	6 (10.0)	9 (13.2)	0.596
Hospitalization for heart failure	1 (1.7)	1 (1.5)	0.930
Myocardial infarction	4 (6.7)	5 (7.4)	0.579
PMI	3 (5.0)	5 (7.4)	0.722
Stent thrombosis	2 (3.3)	0 (0)	
Target vessel revascularization	1 (1.7)	3 (4.4)	0.703
Cardiovascular death	2 (3.3)	0 (0)	
All-cause death	2 (3.3)	1 (1.5)	0.600

Categorical variables are shown as *n* (%).

PMI, PCI-related myocardial infarction

Figures

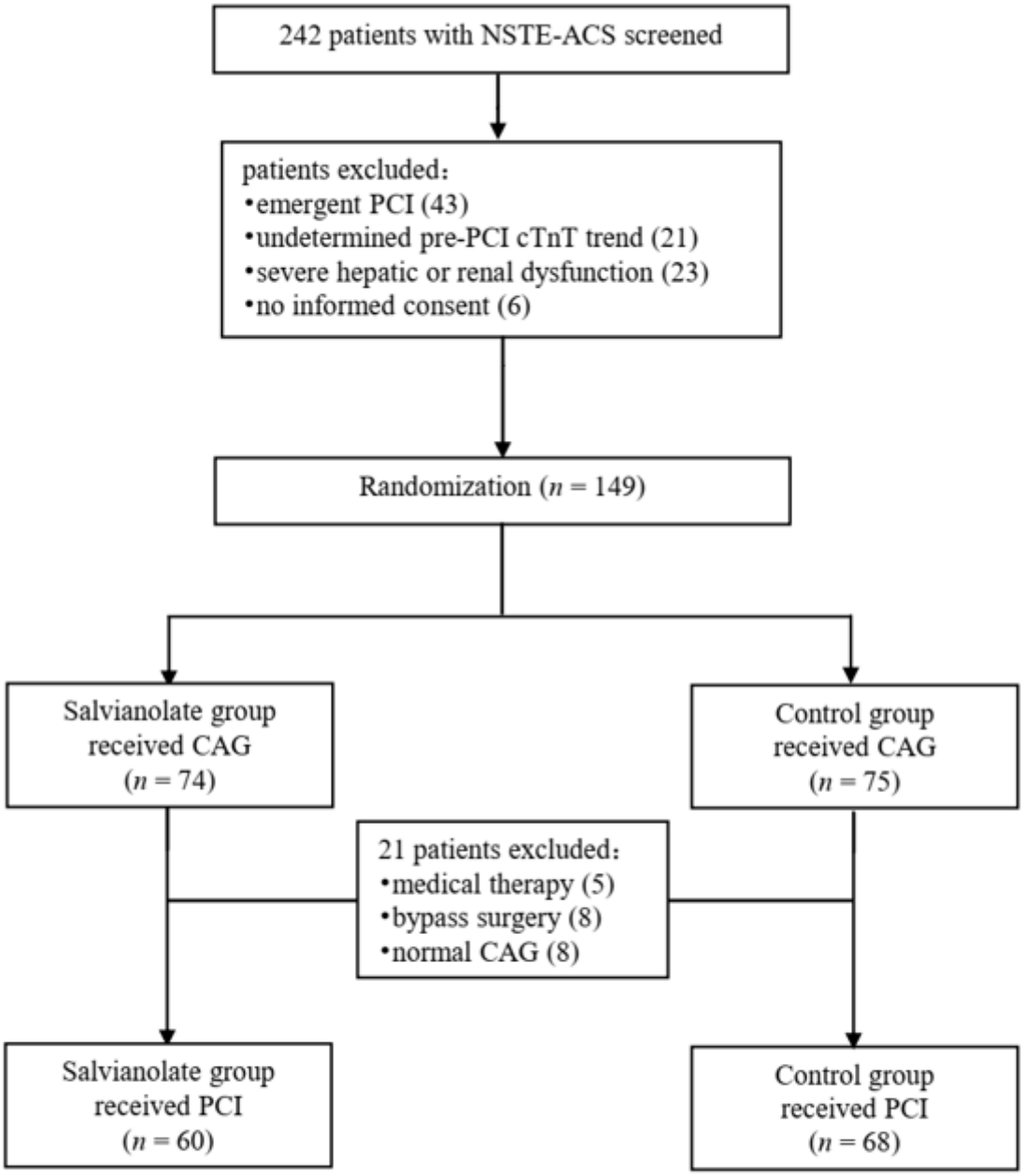

Figure 1

Figure 1

Flow diagram of the study We screened 242 patients with NSTE-ACS undergoing elective PCI from October 2016 to June 2017. Among them, 43 patients were excluded since they received emergent PCI, 21 patients were excluded for pre-procedure abnormal cTnT with undetermined trend, 23 patients were excluded due to severe hepatic or renal dysfunction, and 6 patients were excluded due to lack of informed consent. There are total 149 eligible patients randomized as salvianolate group (n = 74) or control group (n = 75) before procedure. After CAG, 5 patients were excluded due to medical therapy, 8 patients were excluded due to bypass surgery, and additional 8 patients were excluded due to normal CAG. Finally, there

are 60 patients in salvianolate group and 68 patients in control group. CAG, coronary angiography; cTnT, cardiac troponin T; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention

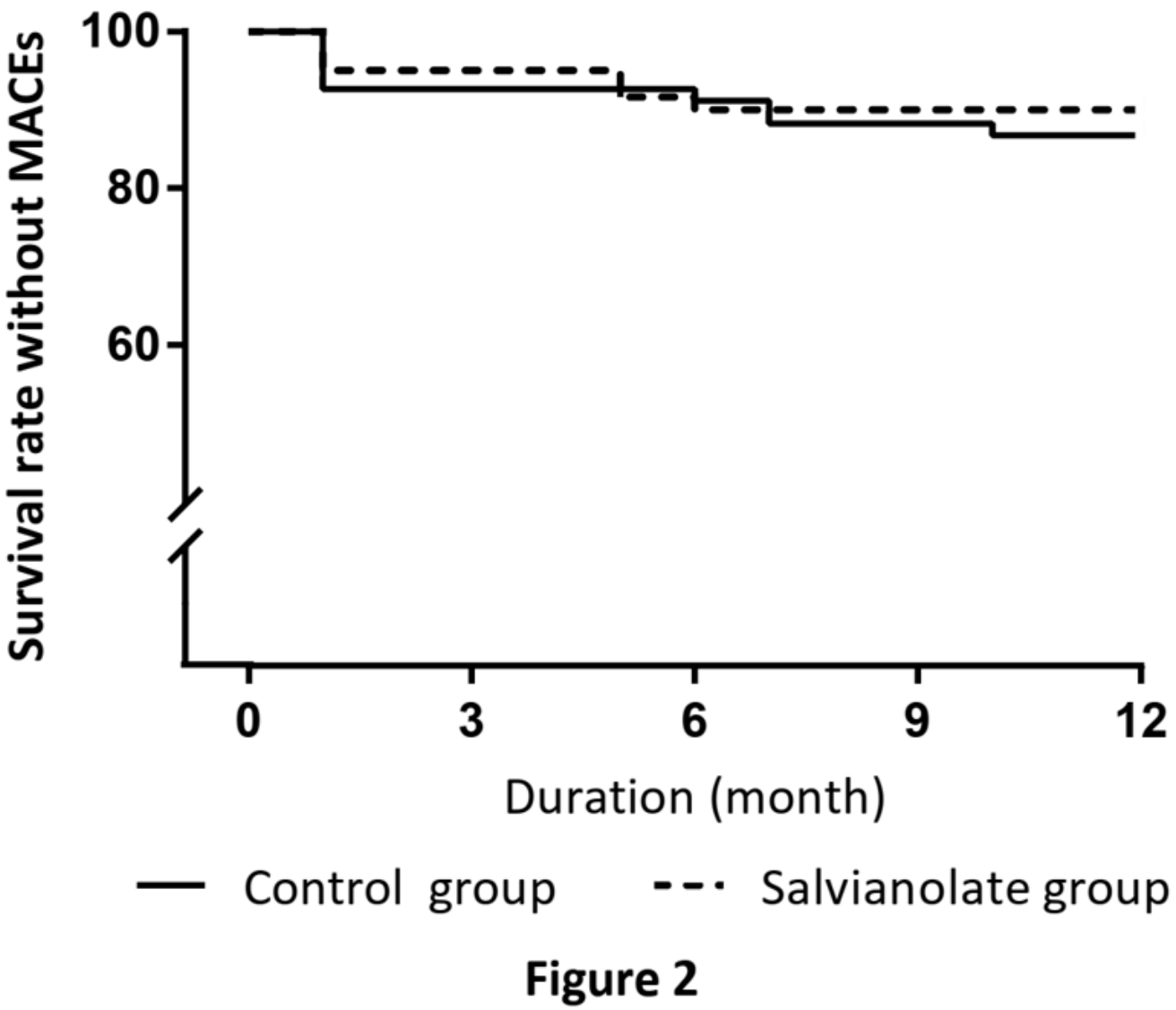

Figure 2

Figure 2

Kaplan-Meier survival curves for one year follow-up without MACEs There was no significant difference between control group and salvianolate group (86.8% vs 90%, p = 0.596) for survival without MACEs for one year follow-up. MACEs, major adverse cardiac events

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010Checklist.pdf