Protective effect of Danhong injection in patients with acute myocardial infarction at a high risk of no-reflow during primary percutaneous coronary intervention

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Abstract

Objective To observe the effect of Danhong injection (DI) in patients with acute ST-segment elevation myocardial infarction (STEMI) at a high risk of no-reflow (NR) during primary percutaneous coronary intervention (PCI). Methods Patients were placed in a DI group and control group. The DI group was given DI and the control group was given physiologic saline. The administration lasted 4 to 6 days in both groups after PCI. Cardiac magnetic resonance (CMR) was carried out during the perioperative period (7 ± 2 days). The primary endpoint of the study was myocardial infarct size (IS) imaged on delayed-enhancement CMR. The secondary endpoint was major adverse cardiac events observed 6 months after PCI. Results In total, 160 high-risk NR patients were enrolled, and 110 patients completed the CMR examination. According to postoperative CMR, the Myocardial Salvage Index and left ventricular ejection fraction were higher in the DI group (0.57 ± 0.13 vs. 0.48 ± 0.17, P < 0.01; 49.3% ± 6.9% vs. 46.2% ± 7.7%, P = 0.03, respectively), whereas the IS was lower (19.7% ± 5.6% vs. 22.2% ± 6.5%, P = 0.04), compared with that in the control group. These differences were observed to be significant. After 6 months, the prevalence of major adverse cardiac events in the DI group decreased compared with that in the control group, but the differences were not observed to be significant (P > 0.05). Conclusion The application of DI can reduce the myocardial infarct size in STEMI patients at a high risk of NR during primary PCI.

Keywords: Cardiac magnetic resonance; Danhong injection; Myocardial infarction; No-reflow risk

1 Introduction

In recent years, the incidence and mortality of acute myocardial infarction (AMI) in China have increased significantly.[1] However, with the emergence of multiple treatment modalities [e.g., percutaneous coronary intervention (PCI)], AMI mortality has decreased from 20% in the late-1980s to 5%–7% today.[2-5]

However, the “no reflow” (NR) phenomenon in primary PCI increases the risk of irreversible damage to the myocardium and coronary microcirculation,[6] resulting in an increase in the final size of the myocardial infarct.[7] Therefore, identifying patients at a high risk of NR using a prediction model with good sensitivity and specificity is important in the prevention and treatment of NR.[8]

Several methods have been employed to determine the extent of MI (contrast echocardiography, cardiac markers, single-photon emission computed tomography (SPECT), positron emission tomography) but they all have advantages and disadvantages. Among them, cardiac magnetic resonance (CMR) is better at identifying small areas of myocardial scars. It has been reported that delayed-enhancement CMR can detect <2 g of an infarcted myocardium, whereas SPECT can detect only ≥10 g of an infarcted myocardium.[9-11] Thus, CMR is a good quantitative method for evaluating the size of a myocardial infarct with high sensitivity and specificity.

Among the factors known to cause NR, ischemia–reperfusion injury (IRI) after revascularization by primary PCI is important. Studies have shown Danhong injection (DI), a systemic and multi-targeted treatment of IRI, could be effi-
cacious and safe in patients with unstable angina treated with PCI.[12] However, the treatment effect of DI in the perioperative period of primary PCI has not been clarified.

We wish to evaluate the perioperative myocardial-protective effect of DI in ST-segment elevation myocardial infarction (STEMI) patients at a high risk of NR undergoing primary PCI. In this prospective, randomized, controlled study, we use a model to predict NR to screen patients, and analyzed myocardial infarct size (IS) and other indicators using CMR.

2 Methods

2.1 Ethical approval of the study protocol

The study protocol was approved by the Ethics Committee of Chinese PLA general hospital (S2016-039-01). Our study was conducted in accordance with the ethical standards formulated in the Helsinki Declaration. The study is registered as ChiCTR1800019451 on www.chictr.org.cn. All patients provided written informed consent.

2.2 Inclusion criteria

The inclusion criteria were patients (1) with the first acute ST elevation myocardial infarction and primary PCI diagnosed from October 2016 to January 2018. Ischemic chest pain lasting $\geq 30$ min, ST segment elevation in 2 or more adjacent leads, limb leads $\geq 0.1$ mV, chest leads $\geq 0.2$ mV, onset within 12 h. (2) With a score $\geq 8$ via no reflow prediction model.

2.3 Exclusion criteria

The exclusion criteria were patients: (1) with a history of MI, coronary-stent implantation or coronary artery bypass grafting; (2) with cardiogenic shock; (3) with chronic kidney disease (stage $\geq 3$); and (4) with advanced malignancy.

2.4 Study population and grouping

One-hundred sixty consecutive patients with a score $\geq 8$[8] diagnosed with STEMI for the first time and who underwent primary PCI between October 2016 and January 2018 at the Chinese PLA General Hospital or Beijing Hospital of Traditional Chinese Medicine affiliated with Capital Medical University (Beijing, China) were selected initially.

After implementation of the exclusion criteria stated above, 110 patients were enrolled finally. We used a stratified randomization method for grouping. There were 57 patients in the DI group (56.8 ± 8.9 years) and 53 patients in the control group (55.4 ± 9.5 years).

2.5 Treatment

DI (National Medicine Permission Number: Z20026866; specification: 10 mL/bottle; Shandong Danhong Pharmaceuticals, Shandong, China) was given to patients in the DI group before primary PCI. The control group was given the same dose of 0.9% saline injection before PCI. These treatments are illustrated in Figure 1.

2.6 Collection of in-hospital clinical data

General clinical data [age, sex, risk factors for coronary artery disease (smoking history: $\geq 1$ cigarette per day at the time of the survey), laboratory examinations] were obtained.

2.7 Coronary angiography and percutaneous coronary angioplasty

The pathway for coronary angiography was the femoral artery or radial artery. Patients underwent primary PCI as required. NR was assessed by a double-blind method using Thrombolysis in Myocardial Infarction (TIMI)[13] and Myocardial Blush Grade (MBG)[14] systems. NR was defined as a TIMI flow grade $< 3$, MBG grade $\leq 1$ with exclusion of thrombi, dissection, and spasm.[15] According to the number of coronary vessels with stenosis $\geq 50\%$, coronary artery stenosis was divided into single-vessel disease and multiple-vessel disease.

2.8 CMR examination

CMR was performed on a 1.5-T Multiva system (Philips, Healthcare, Suzhou, China), using a dedicated cardiac coil, with respiratory and ECG gating. The patients underwent short axis, 2- and 4-chamber long axis Cine, Short axis T2-weighted short tau inversion recovery turbo spin echo sequence and late gadolinium enhancement (LGE).

2.8.1 Analyses of images

Images were measured and evaluated by two experienced radiologists with expertise in the diagnosis of cardiac disorders using magnetic resonance imaging. We employed cvi42 (Circle Cardiovascular Imaging, Calgary, AB, Canada) post-processing software. These radiologists traced (manually) the edge outlining the endocardium, epicardium, hyper-intense areas (Figure 2A), delayed-enhancement lesions (Figure 2B), and hypo-intense areas (Figure 2C) in left-ventricular short-axis images slice-by-slice using cvi42 software. Myocardial area at risk (AAR) and IS of the left ventricle could be obtained. The same two experienced CMR readers validated the method used to assess intra- and interobserver variability were 0.01 ± 0.03 and 0.02 ± 0.05, respectively.
Figure 1. **Treatment schedule.** CK-MB: creatine kinase MB; CMR: Cardiac magnetic resonance; cTnT: cardiac Troponin T; NR: no reflow; PCI: percutaneous coronary intervention.

Figure 2. **T2-weighted and delayed enhancement images.** (A): The area of high intensity indicated by the blue arrow is the area of myocardial edema (i.e., myocardial area at risk); (B): the white area of high intensity indicated by the blue arrow is delayed enhancement (i.e., area of myocardial infarction size); (C): The area of hypo-enhancement within the hyper-enhanced area indicated by the yellow arrow denotes microvascular obstruction (i.e., area of microvascular obstruction).

The myocardial AAR, IS and microvascular obstruction (MVO) were measured. Briefly, the AAR was obtained by measuring the area of edema in the T2-weighted inversion sequence of CMR images using cvi42 software (Figure 2A). AAR was defined as the hyper-intense area on T2-weighted images, expressed in percentage of the total LV mass. Delayed-enhancement images were obtained about 8 min after intravenous injection of 0.1 mmol/kg body weight gadolin-
iew (Gadovist, Bayer Schering, Belin, Germany). The infarct size was defined as the hyper-enhanced myocardium on the delayed-enhancement images, expressed in percentage of the total LV mass (Figure 2B). The myocardial salvage index (MSI) was calculated using the following equation:

\[ \text{MSI} = \frac{(\text{AAR} - \text{IS})}{\text{AAR}}. \]

MVO was the hypo-intense area within the hyper-intense-infarction region on the delayed-enhancement images (Figure 2C).

We also measured the left ventricular ejection fraction (LVEF). The left ventricular end-diastolic volume (LVEDV) (Figure 3A) and left ventricular end-systolic volume (LVESV) (Figure 3B) were calculated using cvi42 software. Then, we used the following equations:

Left ventricular stroke volume (LVSV) = LVEDV − LVESV
LVEF = LVSV/LVEDV \times 100%

2.9 Follow-up study

The study endpoints were documented at outpatient follow-up and by telephone 6 months after PCI. Major adverse cardiovascular events were defined as recurrent myocardial infarction, heart failure, repeat revascularization, and cardiac death.

2.10 Statistical analyses

Statistical analyses were carried out using SPSS 21.0 (IBM, Armonk, NY, USA). Continuous variables data are described as the mean ± SD. Continuous variables were analyzed by the Student’s t-test (if a normal distribution) or Mann-Whitney U-test (if not normally distributed). Categorical variables are described as percentages and were analyzed by the χ² test or Fisher’s exact test for univariate analysis. \( P < 0.05 \) was considered significant.

3 Results

3.1 Enrollment and demographic data

A total of 295 STEMI patients were screened for the present study and 135 patients did not meet the inclusion criteria. The remaining 160 patients were assigned randomly to receive DI or a placebo injection. Finally, 110 patients underwent CMR. Among them, 90 patients underwent CMR in the Chinese PLA General Hospital and the other 20 in the Beijing Hospital of Traditional Chinese Medicine affiliated with Capital Medical University.

3.2 Comparison of clinical characteristics at baseline

There were no significant differences between the DI group and control group (\( P > 0.05 \) for all) with respect to their clinical characteristics at baseline (Table 1). Hence, the two groups were comparable in this regard.

3.3 PCI characteristics

There was no significant difference in the infarct-related artery and incidence of no reflow in coronary angiography between the two groups after PCI (\( P > 0.05 \) for all). Hence, the two groups were comparable with regard to PCI characteristics (Table 2).

3.4 Detection of myocardial enzymes

Before PCI, the mean level of creatine kinase MB (CK-MB) and cardiac troponin T (cTnT) in the DI group and control group was similar (\( P > 0.05 \) (Table 3). After PCI, the level of CK-MB and cTnT had increased in both groups, but the change in the DI group was significantly lower than that in the control group. All of these differences were significant (\( P < 0.05 \) (Table 3).

![Figure 3](http://www.jgc301.com; jgc@jgc301.com | Journal of Geriatric Cardiology)

Figure 3. Cine still-frame images. (A): Left ventricular end-diastolic volume measurement on CMR. The green line is the left ventricular epicardium and the red line is the left ventricular endocardium. (B): Left ventricular end-systolic volume measurement on CMR. The green line is the left ventricular epicardium and the red line is the left ventricular endocardium. CMR: cardiac magnetic resonance.
### Table 1. Clinical characteristics of patients at baseline.

|                      | DI group \((n = 57)\) | Control group \((n = 53)\) | \(P\) value |
|----------------------|------------------------|-----------------------------|-------------|
| Age, yrs             | 56.8 ± 8.9             | 55.4 ± 9.5                  | 0.06        |
| Male                 | 48 (84.2%)             | 47 (88.7%)                  | 0.49        |
| Diabetes             | 14 (24.6%)             | 11 (20.8%)                  | 0.63        |
| Hypertension         | 30 (52.6%)             | 22 (41.5%)                  | 0.24        |
| Hyperlipidemia       | 15 (26.3%)             | 22 (41.5%)                  | 0.09        |
| Smoking history      | 28 (49.1%)             | 35 (66%)                    | 0.07        |
| CHD family history   | 6 (10.5%)              | 10 (18.9%)                  | 0.22        |
| BMI, kg/m²           | 25.3 ± 3.0             | 25.4 ± 2.8                  | 0.47        |
| Heart rate, beats/min| 75.1 ± 13.8            | 79.1 ± 13.0                 | 0.10        |
| Systolic pressure, mmHg | 123.6 ± 22.7          | 125.1 ± 22.1                | 0.19        |
| Diastolic pressure, mmHg | 78.8 ± 16.5           | 74.6 ± 16.8                 | 0.28        |
| Plasma glucose, mmol/L | 9.9 ± 3.8              | 9.8 ± 3.9                   | 0.89        |
| LDL-C, mmol/L        | 3.3 ± 0.9              | 3.1 ± 0.6                   | 0.81        |
| HDL-C, mmol/L        | 0.9 ± 0.3              | 1.2 ± 0.3                   | 0.64        |
| TG, mmol/L           | 1.2 ± 0.7              | 1.4 ± 1.0                   | 0.14        |
| Serum creatinine, μmol/L | 75.6 ± 12.2           | 74.8 ± 14.9                 | 0.82        |
| ACEI/ARB             | 13 (22.8%)             | 17 (32.1%)                  | 0.28        |
| β-blockers           | 45 (78.9%)             | 36 (67.9%)                  | 0.19        |
| Statin               | 55 (96.5%)             | 50 (94.3%)                  | 0.93        |
| Door to balloon time, min | 72.1 ± 20.3           | 67.8 ± 12.3                 | 0.85        |
| GPlIB/IIIa antagonist | 50 (94.3%)             | 53 (93%)                    | 1.00        |
| LVEDV, mL            | 98.4 ± 15.9            | 92.6 ± 14.0                 | 0.12        |
| LVESV, mL            | 47.2 ± 10.6            | 46.4 ± 9.7                  | 0.67        |
| LVEF (%)             | 53.5% ± 7.5%           | 50.0% ± 6.2%                | 0.02*       |

Data are presented as mean ± SD or \(n\) (%). *\(P < 0.05\) was considered significant. Medications were used only during the perioperative period. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor antagonist; BMI: body mass index; CHD: coronary heart disease; DI: Danhong injection; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVEF: left ventricular ejection fraction; TG: triglyceride.

### Table 2. PCI characteristics.

|                      | DI group \((n = 57)\) | Control group \((n = 53)\) | \(P\) value |
|----------------------|------------------------|-----------------------------|-------------|
| Infarct-related artery |                        |                             | 0.91        |
| Anterior descending  | 25 (43.9%)             | 24 (45.3%)                  |             |
| Circumflex artery    | 8 (14.0%)              | 6 (11.3%)                   |             |
| Right coronary artery| 24 (42.1%)             | 23 (43.4%)                  |             |
| Multiple vessel disease | 17 (29.5%)             | 15 (28.6%)                  | 0.93        |
| Killip I preoperative | 55 (96.5%)             | 51 (96.2%)                  | 1.00        |
| No-reflow postoperative | 8 (14.0%)             | 9 (17.0%)                   | 0.87        |

Data are presented as \(n\) (%). DI: Danhong injection; PCI: percutaneous coronary intervention.

### Table 3. Levels of myocardial enzymes in patients.

|                      | Preoperative | Postoperative peak concentration |
|----------------------|-------------|---------------------------------|
|                      | DI group    | Control group                   | DI group    | Control group |
| CK-MB, ng/mL         | 37.9 ± 23.5* | 35.2 ± 19.0                     | 180.3 ± 139.2* | 257.7 ± 205.3* |
| cTnT, ng/mL          | 1.8 ± 1.2*  | 1.6 ± 1.0                       | 6.4 ± 4.9* | 10.3 ± 7.7*  |

Data are presented as mean ± SD. *\(P < 0.05\), preoperative DI group was compared with the control group; *\(P > 0.05\), postoperative DI group was compared with the control group, *\(P < 0.05\). CK-MB: creatine kinase MB; DI: Danhong injection.
3.5 Post PCI CMR evaluation

Compared with the control group, the DI group had a smaller IS (19.7% ± 5.6% vs. 22.2% ± 6.5%, P = 0.04), higher MSI and LVEF (0.57% ± 0.13% vs. 0.48% ± 0.17%, P < 0.01; 49.3% ± 6.9% vs. 46.2% ± 7.7%, P = 0.03, respectively). The prevalence of MVO was reduced in the DI group (21.1% vs. 39.6%, P = 0.03). There was no significant difference in AAR% between the two groups (47.4% ± 11.2% vs. 43.8% ± 9.8%, P = 0.08). Detailed information is shown in Table 4.

3.6 Major cardiovascular events during follow-up

A total of 98.6% of patients were followed up. During the 6-month period, three patients died of complications related to MI. After 6 months, the prevalence of major cardiovascular adverse events in the DI group were lower than that in the control group. However, there was no significant difference in the prevalence of recurrent MI, revascularization, or cardiac death between the two groups (P > 0.05) (Table 5).

4 Discussion

It is showed that DI may have a role in protecting against MI, decreasing the IS, increasing the MSI, improving cardiac function, and reducing release of the markers of myocardial necrosis in STEMI patients at high risk of NR during the perioperative period of primary PCI.

DI is a herb used in traditional Chinese medicine. The main components are tanshinones and Salvia miltiorrhiza. The active ingredients of DI are mainly salvianolic acid-A, B and hydroxysafflor yellow A.

DI can prevent myocardial IRI in rats in vivo. It exerts prominent anti-inflammatory effects by inhibiting activation of the nuclear factor-kappa B signaling pathway via hydroxysafflor yellow A, and salvianolic acid-B has powerful antioxidative capacity because it increases nuclear factor-2 expression.

In vitro, DI has a protective effect against the myocardial-cell injury induced by hypoxia–reperfusion and hydrogen peroxide because it can inhibit opening of mitochondrial permeability transition pores by mitigating Ca2+ overload and generation of reactive oxygen species in myocardial cells.

Recent study showed that patients with acute coronary syndrome treated with DI combined with Naoxintong capsule for 3 months after hospital discharge demonstrated better improvement in cardiac function than that in a control group. Another clinical study focusing on the perioperative period of PCI concluded that DI can improve myocardial injury and cardiac systolic function. Therefore, there is a clear theoretical basis and clinical evidence to suggest that DI can improve IRI.

Our study elicit similar results to the findings mentioned above. Patients in the DI group have a higher LVEF and lower peak levels of myocardial-necrosis markers after primary PCI than those in the control group, and these differences were significant.

We use CMR to determine the area of MI. A paramagnetic contrast agent—gadolinium—was applied to produce a bright image in the myocardium given its delay when passing in and out of infarcted cardiomyocytes. Several studies have found almost identical agreement between the range of delayed enhancement and the histopathologic area of MI. The myocardial AAR is defined as the area where the myocardial ischemia occurs at the time of coronary occlusion (i.e., myocardial edema). Experimental studies have shown that myocardial edema is closely related to the myocardial AAR as determined by histology. The ratio of the IS to the myocardial AAR determines the MSI.

Some clinical studies have suggested that if CMR is undertaken < 3 days after STEMI, the IS would be overestimated and the myocardial AAR would be underestimated. If CMR is carried out > 5 days after STEMI, the edema-based myocardial AAR may be underestimated. Therefore, 3–5
days after STEMI may be the optimal time to undertake CMR. Considering that the patients enrolled in our study were at high risk of NR and their conditions were relatively complex, CMR was done 5–9 days after PCI to assess the changes in necrosis and edema of myocardial tissue accurately.

In the present study, the NR prevalence upon immediate coronary angiography showed no significant difference in the target vessels of the two groups. The MVO prevalence was reduced significantly in the DI group when using high-resolution CMR to identify NR. Durante and colleagues pointed out that, after primary PCI in STEMI patients, the prevalence of major cardiovascular events at 5 years in patients with MVO was significantly higher than that in patients with angiographic NR without MVO. That is, MVO can be used to diagnose microcirculatory obstacles accurately.

By identifying NR with MVO, we found that DI could reduce the prevalence of microcirculatory obstacles in high-risk NR patients. Patients in the DI group had improved IS, MSI and LVEF compared with those in the control group. Hence, DI reduced the IS and improved LVEF.

There was no significant difference in the myocardial AAR between the two groups, which may have been related to the time selected for postoperative examination. In some patients, the time taken for CMR examination exceeds the optimal period for edema identification suggested in the literature, which may affect identification of myocardial edema. Comparison of preoperative and postoperative data of primary PCI between the two groups revealed that DI could reduce the release of myocardial-necrosis markers significantly. There was no significant difference in the prevalence of major adverse cardiac events between the two groups during 6-month follow-up, which may have been related to the short follow-up period, but the prevalence was lower in the DI group than that in the control group.

There are limitations in our study. The study cohort was small as the tolerance of CMR was poor.

In conclusion, application of DI in STEMI patients during the perioperative period of primary PCI can reduce the IS, as well as increase the MSI and LVEF. CMR can be used to calculate the IS and LVEF accurately. CMR can be employed to identify the MVO area, and to detect the NR area sensitively. A multi-center, large-scale clinical study should be undertaken to corroborate our observations.

Acknowledgments

This study was supported by grant from the Capital Health research and development of special project (2016-1-5011). The authors had no conflicts of interests to disclose.

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