Effect of Shenfu Injection on Reperfusion Injury in Patients Undergoing Primary Percutaneous Coronary Intervention for ST Segment Elevation Myocardial Infarction: A Pilot Randomized Clinical Trial

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Background: Shenfu injection is a traditional Chinese medicine formulation that alleviates ischemia-reperfusion injury through multiple pharmacologic effects. However, no data are available regarding its efficacy in patients with myocardial infarction. We aimed to examine the effects of Shenfu injection on infarct size in patients with ST segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI).

Methods: From April 2016 to February 2018, 40 patients with first-time anterior STEMI undergoing primary PCI within 6 h of symptom onset were randomized 1:1 to intravenous Shenfu injection (80 ml Shenfu injection + 70 ml 5% glucose injection) or placebo (150 ml 5% glucose injection) before reperfusion. Treatment started before PCI and maintained for 5 days after PCI. The primary end point was infarct size assessed by CK-MB area under the curve (AUC) over 72 h and cardiac magnetic resonance (CMR) imaging 4 ± 1 days after PCI.

Results: Infarct size by area under the curve for CK-MB over 72 h did not differ between the Shenfu injection and placebo groups (5602.5 [3539.4–7526.4] vs. 6403.2 [2234.4–8340.6] ng·h/ml, P = 0.82). Among 32 patients who underwent CMR Imaging, a nominal reduction in infarct size was observed in the Shenfu injection group compared with the placebo group (23.9 [15.2–28.5] % vs. 27 [21.9–31.9] %, P = 0.42). After excluding patients with no or minimal infarct, there was a trend toward reduction in infarct size in the Shenfu injection group (24.1 [20.3–29.3] % vs. 29.1 [24.5–32] %, P = 0.18). Incidence of adverse events was similar between the groups.
Conclusions: This pilot study showed that the use of Shenfu injection was safe but did not reduce infarct size by CMR Imaging and CK-MB release kinetics in reperfused patients with STEMI. Larger studies (confining to patients with extensive infarct size) to evaluate the efficacy of Shenfu injection on reperfusion injury are warranted.

Clinical Trial Registration: clinicaltrials.gov, identifier: NCT02709798.

Keywords: myocardial infarction, primary percutaneous coronary intervention, reperfusion injury, Shenfu injection, cardiac magnetic resonance imaging

INTRODUCTION

The introduction of primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI) allows timely reperfusion for limiting infarct size and subsequent cardiac remodeling (1). However, reperfusion per se can trigger irreversible myocardial injury, a phenomenon called reperfusion injury. Many cardioprotective therapies have been proposed to reduce infarct size but have shown inconsistent clinical efficacy (2).

Shenfu injection is a traditional Chinese medicine formulation containing ginseng (Panax; family: Araliaceae) and aconite (Radin aconiti lateralis preparata, Aconitum carmichaeli Debx; family: Ranunculaceae), with ginsenosides and aconite alkaloids as the main active ingredients (3, 4). Its quality is strictly controlled in compliance with the standard of the China Ministry of Public Health (official approval code: certification number Z20043117; No. 110804, Yaan, China) (3). Animal studies have shown that Shenfu injection has protective effects against reperfusion injury through multiple pharmacologic effects, such as scavenging free radicals, inhibiting inflammatory mediators, suppressing cell apoptosis, and inhibiting calcium overload (5–7). However, no data are available regarding its efficacy in patients with myocardial infarction. We aimed to determine whether the use of Shenfu injection, as compared to placebo, might reduce infarct size in patients with STEMI undergoing primary PCI.

METHODS

Study Design and Participants

This was a single-center, randomized, blinded, placebo-controlled pilot study. From April 2016 to February 2018, patients aged 18 to 75 years with first-time anterior STEMI and scheduled for primary PCI within 6 h of symptom onset were eligible for enrollment. STEMI was diagnosed according to the third universal definition or myocardial infarction (8). An additional inclusion criterion was the presence of proximal or middle left anterior descending (LAD) occlusion with pre-PCI TIMI flow 0 or 1. Major exclusion criteria included patients with prior myocardial infarction and cardiogenic shock, and those receiving thrombolytic therapy. This study was conducted in accordance with the amended Declaration of Helsinki. The Institutional Review Board of Beijing Anzhen Hospital, Capital Medical University approved this study [D99-2015(043)-TCM-4]. All the patients provided written informed consent.

Randomization, Intervention, and Outcomes

Eligible patients were randomized 1:1 to intravenous Shenfu injection (n = 20, 80 ml Shenfu injection + 70 ml 5% glucose injection) or matched placebo (n = 20, 150 ml 5% glucose injection) before reperfusion. The production process of Shenfu injection has been described elsewhere (9, 10). After informed consent was obtained, a blinded study medication box was opened. This box contained Shenfu injection or matched placebo (5% glucose injection) and labeled with a number that corresponded with the randomization list. This list was pre-specified as the treatment allocation list with serial numbers of 01 to 40 by Medical Statistics Office of Peking University First Hospital, Beijing, China. Randomization took place without stratification with a block size of 4. Treatment started ≥30 min before PCI and maintained for 5 days (once daily) after PCI (six times in total). Treatment assignment was blinded to both the patients and treating staff.

The primary end point was enzymatic infarct size assessed by creatine kinase-myocardial band (CK-MB) area under the curve (AUC) over 72 h (immediately after admission [0 h], and 6, 12, 18, 24, 48, and 72 h after PCI) and CMR Imaging (percent infarcted myocardium relative to left ventricular [LV] mass) 4 ± 1 days following PCI. Secondary end points included AUC for troponin I (TnI) over 72 h, peak value of CK-MB and TnI within 72 h, complete ST-segment resolution (≥70%) immediately post PCI, LV structure and function (left ventricular end diastolic volume [LVEDV], left ventricular end systolic volume [LVESV], and LV ejection fraction [LVEF]), and major adverse cardiovascular and cerebrovascular events (MACCE, such as death, non-fatal myocardial infarction, target vessel revascularization, stroke, new-onset heart failure during hospitalization, and re-hospitalization for heart failure) through 28 days post PCI. Details of methods, such as CMR Imaging protocol, are provided in Supplementary Material 1.

Sample Size

Sample size calculation was limited considering that the primary outcome for Shenfu injection had not been previously evaluated at the time of the study design. Given the exploratory nature of this pilot study, a total of 40 participants were enrolled to collect
### TABLE 1 Baseline characteristics by treatment assignment.

| Characteristic                        | Overall (N = 40) | Shenfu injection (n = 20) | Placebo (n = 20) | P-value |
|---------------------------------------|------------------|--------------------------|------------------|---------|
| **Demographics**                      |                  |                          |                  |         |
| Age, mean (SD), y                     | 54.4 (10.2)      | 50.4 (10.2)              | 58.4 (8.6)       | 0.01    |
| Male                                  | 35 (87.5)        | 17 (85.0)                | 18 (90.0)        | 1.0     |
| BMI, median (IQR), kg/m²              | 25.9 (23.3–27.0) | 26.0 (23.0–27.7)         | 25.8 (23.3–26.7) | 0.67    |
| **Medical history**                   |                  |                          |                  |         |
| Diabetes                              | 11 (27.5)        | 6 (30.0)                 | 5 (25.0)         | 0.72    |
| Hypertension                          | 27 (67.5)        | 12 (60.0)                | 15 (75.0)        | 0.31    |
| Hyperlipidemia                        | 30 (75.0)        | 17 (85.0)                | 13 (65.0)        | 0.14    |
| Current smoking                       | 25 (62.5)        | 14 (70.0)                | 11 (55.0)        | 0.33    |
| **Clinical presentation**             |                  |                          |                  |         |
| Total ischemic time, mean (SD), min   | 276 (92)         | 274 (92)                 | 278 (95)         | 0.91    |
| Systolic BP, mean (SD), mmHg          | 137.6 (26.9)     | 141.3 (26.0)             | 134.0 (28.0)     | 0.40    |
| Diastolic BP, mean (SD), mmHg         | 84.7 (20.2)      | 88.2 (20.0)              | 81.5 (20.6)      | 0.31    |
| Heart rate, mean (SD), b p m          | 81.9 (13.2)      | 82.1 (11.7)              | 81.8 (14.8)      | 0.95    |
| Killip class I                        | 37 (92.5)        | 18 (90.0)                | 19 (95.0)        | 1.0     |
| **Procedure**                         |                  |                          |                  |         |
| Diseased vessel                       |                  |                          |                  | 0.70    |
| 1 vessel                              | 18 (45.0)        | 11 (55.0)                | 7 (35.0)         |         |
| 2 vessels                             | 12 (30.0)        | 3 (15.0)                 | 9 (45.0)         |         |
| 3 vessels                             | 10 (25.0)        | 6 (30.0)                 | 4 (20.0)         |         |
| PCI                                   | 37 (92.5)        | 18 (90.0)                | 19 (95.0)        | 1.0     |
| Stenting                              | 33 (82.5)        | 16 (80.0)                | 17 (85.0)        | 1.0     |
| TIMI grade 3 post-PCI                 | 37/37 (100%)     | 18/18 (100.0%)           | 19/19 (100.0%)   | -       |
| CTFI post-PCI, median (IQR), frame    | 11 (10–12)       | 11 (10–12)               | 11 (10–12)       | 0.85    |
| Thrombus aspiration                    | 28 (70.0)        | 15 (75.0)                | 13 (65.0)        | 0.49    |
| Glycoprotein IIb/IIIa inhibitors      | 16 (40.0)        | 8 (40.0)                 | 8 (40.0)         | 1.0     |
| **Medication on discharge**           |                  |                          |                  |         |
| Aspirin                               | 38/39 (97.4)     | 20 (100.0)               | 18/19 (94.7)     | 0.49    |
| Thienopyridine                        | 39/39 (100.0)    | 20 (100.0)               | 19/19 (100.0)    | –       |
| Statin                                | 38/39 (97.4)     | 19 (95.0)                | 19/19 (100.0)    | 1.0     |
| β-blockers                            | 37/39 (94.9)     | 19 (95.0)                | 18/19 (94.7)     | 1.0     |
| ACEI/ARB                              | 32/39 (82.1)     | 17 (85.0)                | 15/19 (78.9)     | 0.70    |

ACEI, angiotensin-converting enzymes inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CTFI, corrected TIMI frame count; IQR, interquartile range; PCI, percutaneous coronary intervention; SD, standard deviation; TIMI, thrombolysis in myocardial infarction. Data are presented as mean (SD), median (IQR), n (%), or n/N (%).

preliminary data. After that, statistical analysis will be performed to assess whether the sample size meets the study design and a larger study may be performed.

### Statistical Analyses

Data analyses were performed according to the intention-to-treat concept. In addition, analyses were performed on a per protocol set, excluding major protocol violators. Continuous variables were presented as mean (SD) or median (first and third quartiles), and were compared by Student t-test or Wilcoxon rank sum test. Categorical variables were shown as the number (percentage), and were compared by Chi-square or Fisher exact test when appropriate. Wilcoxon rank sum test or CMH-χ² test was performed for rank data. All the analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC, United States). All the tests were two-sided at a 5% significance level.

### RESULTS

### Study Population and Clinical Characteristics

The flow of patient recruitment is shown in [Supplementary Figure 1](#). Forty patients were randomized, and 32 (80%) completed CMR Imaging. Mean (SD) patient age was 54.4 (10.2) years, and 87.5% of the patients were men. The treatment groups were generally well-matched, although the mean age was younger in the Shenfu injection group (50.4 years) than in the placebo group (58.4 years). The total ischemic time and hemodynamic status (blood pressure, heart rate, and Killip class) were similar between the two groups. The use of stent, thrombus aspiration, glycoprotein IIb/IIIa inhibitors, and antiplatelet therapy was uniformly high in both arms (Table 1).
Efficacy Analysis

Infarct size by AUC for CK-MB was not significantly decreased in the Shenfu injection group compared with the placebo group (intention-to-treat, 5602.5 [3539.4–7526.4] vs. 6403.2 [2234.4–8340.6] ng·h/ml, \( P = 0.82 \); per-protocol, 5902.2 [3960.3–7526.4] vs. 7561.8 [3840.9–8383.5] ng·h/ml, \( P = 0.27 \)) (Figure 1). Likewise, the AUC for TnI was not significantly different in patients who received Shenfu injection compared with those who received the placebo (intention-to-treat, 2317 [1478.9–4498.4] vs. 2832.9 [738.2–6685.8] ng·h/ml, \( P = 0.96 \); per-protocol, 2372.9 [1623.4–4498.4] vs. 3608.3 [1200.6–6686] ng·h/ml, \( P = 0.39 \)) (Supplementary Figure 2). There were no differences between the groups in peak CK-MB (295 [176.3–401] vs. 350.4 [102.2–494.6], \( P = 0.92 \)) and TnI (117.5 [37.9–167] vs. 105 [33–210.6], \( P = 0.79 \)) (Supplementary Figure 2). There were no differences between the groups in peak CK-MB (295 [176.3–401] vs. 350.4 [102.2–494.6], \( P = 0.92 \)) and TnI (117.5 [37.9–167] vs. 105 [33–210.6], \( P = 0.79 \)) levels. The rate of complete ST-segment resolution (\( \geq 70\% \)) was similar between the groups (36.8% vs. 38.9%, \( P = 0.9 \)). Also, there were no differences between the groups in levels of high-sensitivity C-reactive protein 24 (227 [141–380] vs. 292.5 [147–452], \( P = 0.68 \)) and 72 h (155 [64–237] vs. 180 [117–307], \( P = 0.72 \)) after primary PCI.

Cardiac MRI was performed at a median of 4 (4 to 5) days after PCI. A nominal reduction in infarct size was observed in the Shenfu injection group compared with placebo group (23.9 [15.2–28.5] % vs. 27 [21.9–31.9] %, \( P = 0.42 \)) (Figure 1 and Table 2). In the per-protocol analysis (sensitivity analysis), after excluding patients with no or minimal infarct (infarct size < 1%), there was a trend toward reduction in infarct size in the Shenfu injection group (24.1 [20.3–29.3] % vs. 29.1 [24.5–32] %, \( P = 0.18 \)) (Figure 1). The LV (LVEDV, LVESV, and LVEF) and other CMR Imaging parameters did not differ significantly between the groups (Table 2).

Clinical and Safety Outcomes

There was one ventricular fibrillation in the Shenfu injection group and one in the placebo group during primary PCI. One patient who received Shenfu injection underwent target vessel revascularization (coronary artery bypass graft) 22 days after PCI (non-treatment-related). Incidence of adverse events was similar between the groups (20 vs. 30%, \( P = 0.72 \)) (Table 3). Moreover, Shenfu injection was not associated with an improvement in quality of life by the Myocardial Infarction Dimensional Assessment Scale (MIDAS) score at 28 days (60 [54–65] vs. 59 [48–63], \( P = 0.33 \)).

DISCUSSION

In this randomized trial of patients with first-time anterior STEMI undergoing primary PCI, the administration of Shenfu injection did not reduce infarct size, as assessed by CMR and CK-MB release kinetics. In the sensitivity analysis,
Table 2 | Cardiac magnetic resonance imaging analysis 4+1 days post percutaneous coronary intervention.

| Characteristic | Overall (N = 40) | Shenfu injection (n = 20) | Placebo (n = 20) | P-value |
|---------------|------------------|--------------------------|------------------|---------|
| CMR performed | 32 (80.0)        | 16 (80.0)                | 16 (80.0)        | 1.0     |
| CMR analyzed  | 32 (80.0)        | 16 (80.0)                | 16 (80.0)        | 1.0     |
| CMR time from PCI, median (IQR), days | 4 (4–5) | 4 (4–5) | 4 (4–5) | 0.70 |
| Infarct size\(^a\), median (IQR), % | 26.0 (20.4–31.5) | 23.9 (15.2–28.5) | 27.0 (21.9–31.9) | 0.42 |
| LV mass, median (IQR), g | 144.0 (124.0–182.5) | 152.9 (131.2–177.4) | 137.6 (120.2–189.6) | 0.56 |
| Area at risk (edema mass)\(^a\), median (IQR), % | 41.7 (27.0–50.3) | 39.9 (26.7–47.9) | 47.9 (29.8–66.2) | 0.36 |
| Myocardial salvage index, median (IQR), % | 41.9 (20.9–54.4) | 40.4 (12.9–63.2) | 41.9 (34.8–45.3) | 0.98 |
| MVO prevalence, % | 24/32 (75.0) | 12/16 (75.0) | 12/16 (75.0) | 1.0 |
| MVO mass\(^a\), median (IQR), % | 1.77 (0.01–3.02) | 1.90 (0.01–3.11) | 1.33 (0.07–2.96) | 0.86 |
| IMH prevalence, % | 17/32 (53.1) | 10/16 (62.5) | 7/16 (43.8) | 0.29 |
| IMH mass\(^a\), median (IQR), % | 0.31 (0.00–3.17) | 1.08 (0.00–3.37) | 0.00 (0.00–2.80) | 0.45 |
| LVEDV, mean (SD), ml | 88.9 (27.4) | 94.8 (27.5) | 82.9 (26.8) | 0.23 |
| LVESV, mean (SD), ml | 46.7 (23.0) | 50.5 (23.8) | 42.9 (22.3) | 0.36 |
| LVEF, mean (SD), % | 49.6 (12.3) | 48.7 (12.4) | 50.5 (12.5) | 0.69 |

CMR, cardiac magnetic resonance; IMH, intramyocardial hemorrhage; IQR, interquartile range; LV, left ventricular; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; MVO, microvascular obstruction; PCI, percutaneous coronary intervention; SD, standard deviation; TIMI, Thrombolysis In Myocardial Infarction. Data are presented as mean (SD), median (IQR), n (%), or n/N (%). \(^a\)Expressed as a percentage of LV mass.

Table 3 | Safety outcomes.

| Events                      | Shenfu injection (n = 20) | Placebo (n = 20) | P-value |
|-----------------------------|---------------------------|------------------|---------|
| Severe adverse events       | 0                         | 0                |         |
| Total number of adverse events | 4 (20%)                  | 6 (30%)          |         |
| Fever                       | 1                         | 1                |         |
| Nausea                      | 0                         | 1                |         |
| Liver injury                | 1                         | 0                |         |
| Renal disorder              | 0                         | 2                |         |
| Urinary tract infection     | 1                         | 0                |         |
| Hypokalemia                 | 0                         | 2                |         |
| Hyperhomocysteinemia        | 1                         | 1                |         |

As a Chinese herbal formula, Shenfu injection is characterized by multicomponents and multiple pharmacologic effects (13). In a recent multicenter randomized trial, Zhang et al. (9) demonstrated that Shenfu injection in combination with conventional post resuscitation care bundle treatment significantly improved survival in patients with return of spontaneous circulation after in-hospital cardiac arrest, probably by scavenging reactive oxygen species and inhibiting calcium overload and cardiomyocyte apoptosis (13). Animal studies have also confirmed the protective effects of Shenfu injection against ischemia-reperfusion injury through the aforementioned mechanisms (3–7).

In this study, we only enrolled patients with large anterior STEMI and within 6 h of onset with occlusion of the proximal/mid LAD, thereby representing a subset most likely to benefit from an adjunct therapy to primary PCI. Also, the drug infusion covered all the reperfusion phases (30 min before PCI and up to 5 days after PCI) to ensure adequate therapeutic levels. Although the primary analysis was non-significant, in patients with extensive infarct (excluding patients with no or minimal infarct), there was a trend toward reduction in CMR Imaging infarct size in the Shenfu injection group compared with placebo group. The results of our study need to be validated in larger trials (particularly confining to patients with estimated larger infarct size).

Study Limitations

Our study has some limitations. First, the sample size was small. Thus, the power to examine the efficacy of intervention was limited. Second, 20% of the patients did not undergo CMR Imaging for primary outcome analysis. Third, we evaluated only a single dose of Shenfu injection and cannot exclude different results with varying dose regimens.

by excluding patients with no or minimal infarct, there was a nominal 5% median reduction in CMR Imaging infarct size in the Shenfu injection group compared with placebo group.

Theoretically, the mechanisms underlying myocardial reperfusion injury are multifactorial, with multiple pathophysiological factors (such as oxidative stress, calcium overload, inflammation, and cell apoptosis) (11). A combining therapy to target different signaling pathways may provide more effective cardioprotection than a single targeted approach. Recently, the (12) NAC in Acute Myocardial Infarction (NACIAM) study demonstrated that the combined use of N-acetylcysteine and nitroglycerin before primary PCI reduced CMR Imaging-assessed infarct size by >30%.
CONCLUSIONS
In this pilot study on patients with first-time anterior STEMI undergoing primary PCI, treatment with Shenfu injection was safe but was not associated with reduction in infarct size as assessed by CMR Imaging and CK-MB release kinetics. Larger studies (confining to patients with extensive infarct size) to evaluate the efficacy of Shenfu injection on reperfusion injury are warranted.

DATA AVAILABILITY STATEMENT
The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT
The studies involving human participants were reviewed and approved by Institutional Review Board of Beijing Anzhen Hospital, Capital Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS
XW and SN: conception, design, data analysis, and interpretation. XM and SN: administrative support. XW, HM, YY, and SN: provision on study materials or patients.

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SUPPLEMENTARY MATERIAL
The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.736526/full#supplementary-material
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