Efficacy and Safety of Combination Therapy of Shenfu Injection and Postresuscitation Bundle in Patients With Return of Spontaneous Circulation After In-Hospital Cardiac Arrest: A Randomized, Assessor-Blinded, Controlled Trial

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Objectives: Postresuscitation care bundle treatment after return of spontaneous circulation in patients experiencing in-hospital cardiac arrest can improve patients' survival and quality of life. The aim of the study was to evaluate the efficacy and safety of combined therapy of Shenfu injection and postresuscitation care bundle in these patients.

Design: Prospective, randomized, controlled clinical study.

Setting: Fifty hospitals in China.

Patients: Adult patients had experienced in-hospital cardiac arrest between 2012 and 2015.

Interventions: Based on the standardized postresuscitation care bundle treatment, patients were randomized to a Shenfu injection group (Shenfu injection + postresuscitation care bundle) or control group (postresuscitation care bundle) for 14 days or until hospital discharge. In the Shenfu injection group, 100 mL Shenfu injection was additionally administered via continuous IV infusion, bid.

Measurements and Main Results: The primary outcome was 28-day survival after randomization. The secondary outcomes included 90-day survival as well as the duration of mechanical ventilation and the hospital stay and the total cost of hospitalization. Of 1,022 patients enrolled, a total of 978 patients were allocated to the two groups: the control ($n = 486$) and Shenfu injection ($n = 492$) groups. The Shenfu injection group had a significantly greater 28-day survival rate (42.7%) than the control group (30.1%). Also, the Shenfu injection group had a significantly higher survival rate at 90 days (39.6%) than the control group (25.9%). Compared with patients in the control group, patients in the Shenfu injection group had lower risks of 28-day mortality (hazard ratio, 0.61; 95% CI, 0.43–0.89; $p = 0.009$) and 90-day mortality (hazard ratio, 0.55; 95% CI, 0.38–0.79; $p = 0.002$). In the Shenfu injection group, the duration of mechanical ventilation (8.6 ± 3.2 vs 12.7 ± 7.9 d; $p < 0.001$) and the hospital stay (8.7 ± 5.9 vs 13.2 ± 8.1 d; $p < 0.001$) were significantly less than in the control group. Irreversible brain damage was the main cause of death in both groups. No serious drug-related adverse event was recorded.

Conclusions: This study demonstrates that Shenfu injection in combination with conventional postresuscitation care bundle treatment is effective at improving clinical outcomes in patients with return of spontaneous circulation after in-hospital cardiac arrest. (*Crit Care Med* 2017; XX:00–00)

Key Words: in-hospital cardiac arrest; postcardiac arrest syndrome; postresuscitation care bundle; Shenfu injection

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Despite the development of resuscitation protocols and increasing knowledge about cardiopulmonary resuscitation, in-hospital cardiac arrest (IHCA) remains associated with significant morbidity and mortality (1). Although the majority of CA patients die during the acute event, a substantial proportion of CA-related deaths occur after return of spontaneous circulation (ROSC) and can be attributed to the development of post-CA syndrome (PCAS) (2, 3). There is growing recognition that postresuscitation care bundle (PRCB) treatment, which encompasses a bundle

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of procedures including targeted temperature management, airway and ventilation management, hemodynamic management, early coronary angiography, and comprehensive critical care, can improve patient outcomes (inhospital standardized treatment plan after ROSC are shown in Supplemental Digital Content 1, section III, http://links.lww.com/CCM/C671) (4, 5).

Traditional Chinese medicine (TCM) goes back over 1,000 years and remains one of the mainstay treatments in China (6). Shenfu injection (SFI), produced by using multistage counter current extraction and macroporous resin adsorption technology, is a well-known TCM formulation containing ginseng (*Panax*; family: Araliaceae) and aconite (Radix aconiti lateralis preparata, Aconitum carmichaeli Debx; family: Ranunculaceae). Ginsenosides and aconite alkaloids are the main active ingredients in Shenfu (7, 8). 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, Ya'an, China) and is ensured by using fingerprint technology during production (chemical and drugs preparation are shown in **Fig. S2** and section IV, Supplemental Digital Content 1, http://links.lww.com/CCM/C671) (8). Recently, a meta-analysis showed that SFI was more effective than conventional therapy in increasing mean arterial pressure, normalizing heart rate, clearing serum lactate, and reducing mortality when treating patients with septic shock (9). Animal experiments have also confirmed that SFI has effects on scavenging free radicals, inhibiting inflammatory mediators, suppressing cell apoptosis, and regulating the host immune response (10–12). As a Chinese herbal formula, SFI is characterized by having multicomponents, multitargets, and multieffects and has been shown to have complex pharmacologic actions (13). As mentioned above, SFI could play a key role in the PRCB, and we hypothesized that combined use of SFI and PRCB treatment may offer more benefits compared with conventional PRCB therapy alone in PCAS. Therefore, we conducted a randomized, assessor-blind, controlled trial to evaluate the efficacy and safety of combination therapy with SFI and PRCB treatment in patients with ROSC after IHCA.

MATERIALS AND METHODS

Design and Setting

Between January 2012 and June 2015, 1,022 consecutive patients with sustained ROSC after CA were enrolled in this randomized, controlled, assessor-blinded, parallel-group trial conducted in 50 hospitals in China. Patients were allocated to two groups: the SFI group, in which the standardized PRCB treatment (**Fig. S1**, Supplemental Digital Content 1, http://links.lww.com/CCM/C671) and SFI were used, and the control group, in which only PRCB treatment was used (4). In the SFI group, 100 mL SFI was administered via continuous IV infusion at a rate of 20 mL/hr, bid for 14 days (SFI preparation is described in Supplemental Materials). The study was approved by the ethics committees of the participating centers, and informed consent was obtained from each participant (or next of kin). Doctors chose medications based on the standardized PRCB treatment and were prohibited from using other additional TCM.

Study Population

Eligible patients had experienced IHCA diagnosed according to the European Resuscitation Council Guidelines for Resuscitation 2010 (4). Both men and women were included. Detailed inclusion/exclusion criteria were reported in the study protocol and are summarized in the Study Protocol (Supplemental Digital Content 2, http://links.lww.com/CCM/C672).

Randomization

The Data Analysis System (DAS) 2.0 statistical software (National Center for Education Statistics, Institute of Education Sciences, Washington, D.C.) was used to generate random numbers. To minimize the impact of the heterogeneity from CA and interhospital variation in patient sources on the results, stratification by investigative center in combination with computer-generated block randomization (block size = 8) according to the sequence of recruitment was employed in the enrollment process. The DAS 2.0 statistical software adopted age and causes of IHCA as the central random control factors to dynamically and randomly allocate the participants, keeping a balance between the two groups to avoid selection bias. Included patients were randomly assigned to the treatment or control group at the ratio of 1:1.

Blinding

Blinding was maintained among the investigators and patients. Investigators and study coordinators were provided with feedback reports indicating the percentage of patients at their local sites that received guideline-based care and potential ways to deliver optimal care based on clinical practice guidelines. Caregivers were not blinded to the intervention, but participants and outcome assessors were blinded to the group assignment.

Concomitant Treatments

All centers were ordered to follow the most recent guidelines regarding initial resuscitation and ICU management (5). When used, therapeutic hypothermia was started immediately at ICU admission (or continued if prehospital-initiated) using external or internal cooling (at the discretion of the center) during the first 24 hours to obtain a target temperature between 32°C and 34°C. Normothermia between 37°C and 37.5°C was then achieved using passive rewarming (0.3°C/hr) and maintained during the next 48 hours. In patients with a high suspicion of acute coronary syndrome as the cause of IHCA, early coronary angiograms were routinely performed at hospital admission and followed, when indicated, by immediate percutaneous coronary interventions (PCIs) (4).

Data Collection and Follow-Up Processes

Information was prospectively collected according to the Utstein recommendations (14). The registry included characteristics such as age, sex, cardiovascular risk factors (hypertension, diabetes mellitus, and current smoking), and initial cardiac rhythm (ventricular fibrillation [VF]/ventricular tachycardia [VT] or pulseless electrical activity [PEA]/asystole). Additional information is available in Supplemental Digital Content 1, section VI, http://links.lww.com/CCM/C671.

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Power Calculation and Statistical Analyses

The sample size was calculated based on the expected reduction in 28-day mortality. We hypothesized that SFI would be beneficial if 28-day mortality could be reduced from 70% to 50%. This hypothesis was generated based on the preliminary clinical results observed in pilot studies (9). We calculated that we would need 290 patients in our primary analysis (145 in each arm) to have 80% power to detect this difference with an α of 0.05. In addition, considering a dropout rate of approximately 20% among randomized patients and the high mortality after ROSC, a total of 500 patients (250 per treatment group) were needed for randomization to achieve the required number of patients for the efficacy analysis. The final study population included a large number of patients and was well balanced. All admitted patients were systematically investigated, provided that they fulfilled the clearly defined inclusion criteria. Under these two assumptions, we recruited 1,022 patients for the study, who were subsequently allocated at a 1:1 ratio to the SFI or control group.

Efficacy was determined by using the per-protocol set (all patients who did not drop out), whereas safety was determined using the safety set (all patients who received at least one dose of SFI). According to Chinese law, all analyses were performed in the modified intention-to-treat population, which was defined as all randomly assigned patients, except for those whose informed consent was impossible to obtain, those whose initial consent was withdrawn, and those who were placed under legal guardianship. Continuous variables were presented as mean ± SD or median (interquartile range), depending on the distribution of the data, and were compared between groups using two-sample *t* test (normal distribution and equal variances assumed) or Mann-Whitney *U* test (nonnormal distribution or equal variances not assumed). Categorical data were presented as counts with frequencies and compared between groups using either chi-square or Fisher exact tests. Both the 28-day and 90-day survival rates were analyzed with the Cochran-Mantel-Haenszel test followed by manual backward-elimination procedures. The Kaplan-Meier method was used to estimate the survival curves, and the log-rank test was used to compare the survival rates between the groups. A Cox proportional hazards regression model was applied to determine the independent contribution of variables for the prediction of 28-day and 90-day mortality. This model assumed that the effect of a variable on the instantaneous death rate was constant over time. This assumption was checked for all predictor variables entered in the model. Stepwise- and backward-selection procedures were used for the Cox regression model to select the variables that were significantly related to death, as assessed by the likelihood ratio test. Hazard ratios (HRs) and 95% CIs were calculated as measures of the clinical impact of the predictor variables. IBM SPSS Statistics, version 22.0 (IBM Corporation, Chicago, IL) was used for statistical analyses. A two-sided significance level of 0.05 was used for statistical inference.

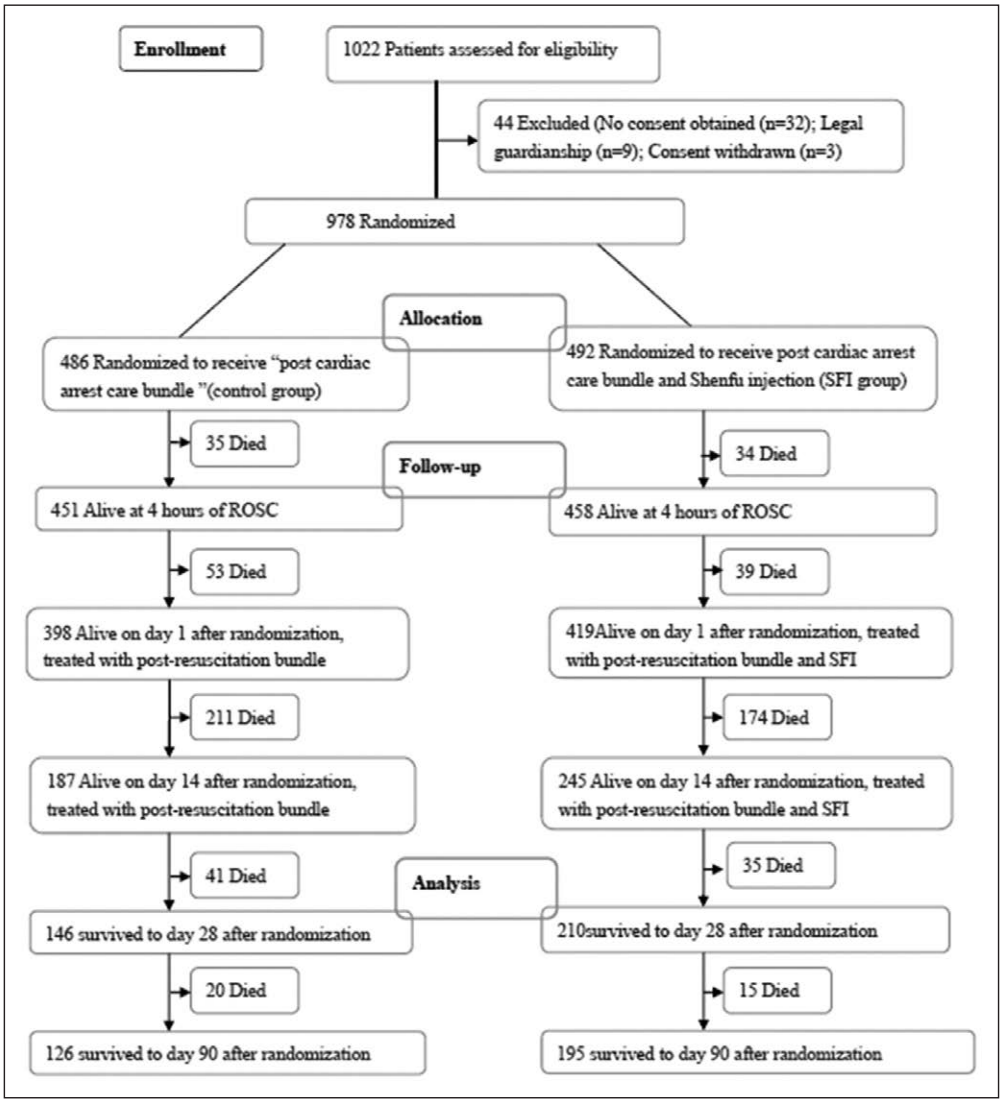

Figure 1. Study flowchart. Flow diagram illustrating the number of patients in each group throughout the study. A total of 1,022 patients were screened for eligibility during the study period. Finally, 978 patients were enrolled in the study, including 492 in the Shenfu injection (SFI) group and 486 in the control group. ROSC = return of spontaneous circulation.

RESULTS

A total of 1,022 consecutive patients with sustained ROSC after CA were recruited between

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January 2012 and June 2015. Data from 44 patients were not analyzed because either the patient's written informed consent could not be obtained after enrollment or was withdrawn. The modified intention-to-treat population (the primary analysis population) consisted of 978 patients, of whom 492 were randomly assigned to the SFI group and 486 to the control group. A flow diagram of patient inclusion is presented in **Figure 1**.

Baseline Characteristics

The distributions of the demographic and clinical characteristics between patients of the SFI and control groups were well balanced and homogeneous (**Table 1**). The mean age was 65.1 years for the SFI group and 64.6 years for the control group, with more than 70% being male. Data for CA initial rhythms and in-hospital treatment are shown in Table 1 and **Table S1** (Supplemental Digital Content 1, http://links.lww.com/CCM/C671). Compared with control patients, SFI patients had a higher mean arterial pressure (MAP) at days 3 and 7 (**Table S2**, Supplemental Digital Content 1, http://links.lww.com/CCM/C671). Within 12 hours after ROSC, all surviving patients were admitted to either the ICUs or coronary care units.

In-hospital treatments, including therapeutic hypothermia and PCI, were equally distributed between the two groups (**Table 2**). At ICU admission, therapeutic hypothermia was used in 93 SFI patients (18.9%) and 87 control patients (17.9%) ($p = 0.69$). The cause of the IHCA was considered of cardiac origin in 480 patients (49.1%), and an early PCI with coronary stenting was performed in 153 patients (31.1%) in the SFI group and 148 of 486 control patients (30.5%; $p = 0.87$) (Table 2). Almost all patients received mechanical ventilation and were severely ill. There were also no significant differences in the causes of death among patients admitted to the ICU, and most deaths were due to brain damage.

Primary Outcome

The SFI group had a significantly greater 28-day survival rate (42.7%), the primary endpoint of this study, compared with the control group (30.1%). The log-rank test revealed a significant difference between the survival curves of these two groups ($p = 0.02$). The Kaplan-Meier plots are shown in **Figure 2*A***.

In addition, patients in the SFI group had a lower risk of a poor outcome during 28-day follow-up (HR, 0.61; 95% CI, 0.43–0.89; $p = 0.009$) (**Table 3**) and were more likely to be alive at hospital discharge with favorable neurologic recovery (143/492 [29.1%] vs 83/486 [17.1%]; $p = 0.03$) compared with those in the control group.

Secondary Outcomes

The cumulative post-CA survival rate at 90 days (second endpoint of this study) was 39.6% for the SFI group versus 25.9% for the control group. At ICU discharge, 70.0% of patients (143/203) in the SFI group reached a Cerebral Performance Category (CPC) score 1 or 2 level (good cerebral performance to moderate cerebral disability) compared with 59.3% of patients (83/140) in the control group ($p = 0.03$). For the long-term survivors, patients in the SFI group had a significantly shorter duration of mechanical ventilation (8.6 ± 3.2 vs 12.7 ± 7.9 d; $p < 0.001$) and hospital stay (8.7 ± 5.9 vs 13.2 ± 8.1 d; $p < 0.001$). Irreversible brain damage was the main cause of death in both groups (64.8% in the SFI group vs 68.0% in the control group; $p = 0.88$) (Table 2).

A Cox proportional hazards regression model was applied to determine the independent contributions of variables to the prediction of 28-day and 90-day death. In the Cox regression analysis, the SFI group had lower risks of 28-day mortality (HR, 0.61; 95% CI, 0.43–0.89; $p = 0.009$) and 90-day mortality

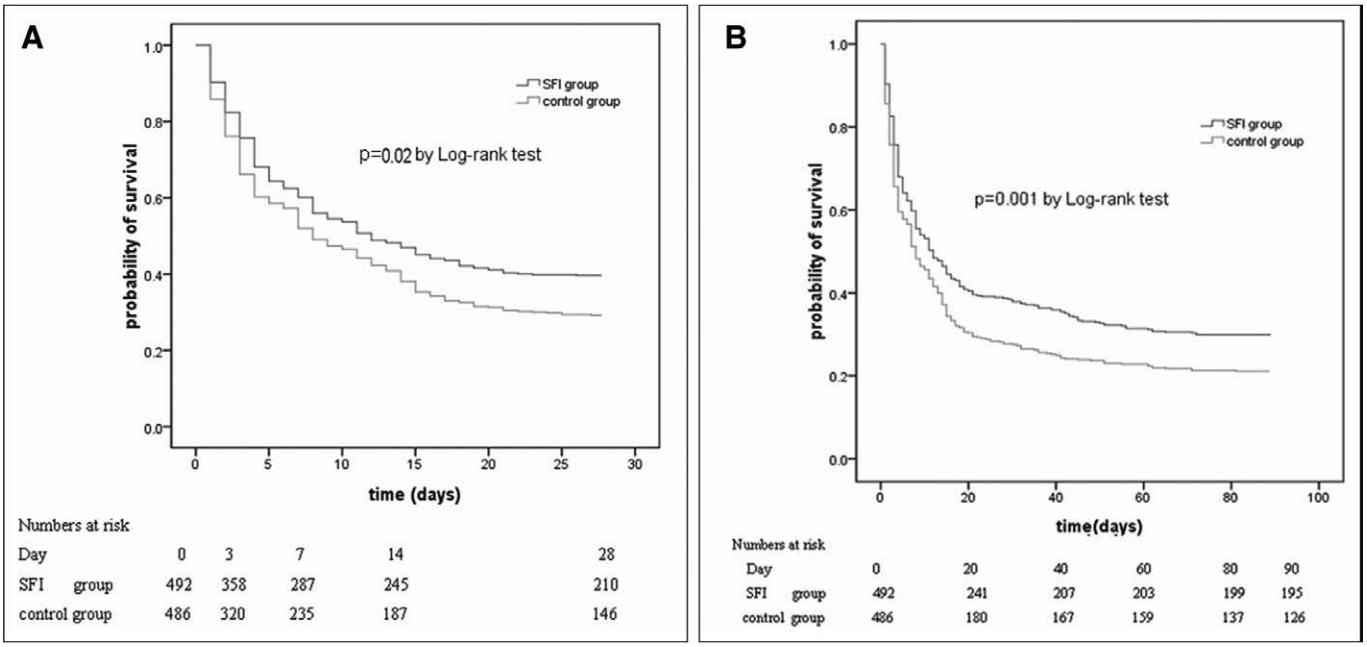

Figure 2. Kaplan-Meier analysis of the probability of survival of patients with post-cardiac arrest syndrome treated with Shenfu injection (SFI) or control (modified intention-to-treat cohort). Probability of survival of patients treated with SFI or control, which was identical to the survival at hospital discharge, at 28 d after randomization (**A**) and at 90 d after randomization (**B**). The numbers of patients at risk were reduced according to the time points of occurrence of patient death.

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TABLE 1. Comparison of Demographic and Basal Clinical Characteristics of Patients Between Shenfu Injection and Control Groups

Characteristic	Shenfu Injection Group (*n* = 492)	Control Group (*n* = 486)	*p*
Demographics			
Age, mean (SD), yr	65.1 (17.4)	64.6 (17.2)	0.60
Male sex, *n* (%)	382 (77.6)	357 (73.5)	0.20
Race, *n* (%)			
Han	458 (93.1)	455 (93.8)	0.74
Other	34 (6.9)	31 (6.2)	0.74
Body mass index, mean (SD)	24.2 (2.1)	24.3 (2.7)	0.56
Cardiovascular history, *n* (%)			
Hypertension	79 (16.1)	78 (16.0)	0.92
Coronary artery disease	158 (32.1)	152 (31.3)	0.74
Cardiac conduction disturbances	46 (9.3)	49 (10.1)	0.36
Cardiac arrhythmia	113 (22.9)	114 (23.4)	0.45
Valvular heart disease	43 (8.7)	42 (8.6)	0.89
Peripheral vascular disease	26 (5.3)	25 (5.1)	0.77
Other chronic comorbidity, *n* (%)	27 (5.5)	26 (5.3)	0.65
Cause of cardiac arrest, *n* (%)			
Cardiogenic shock	137 (27.8)	136 (27.9)	0.78
Acute coronary syndrome	103 (20.9)	104 (21.4)	0.56
Respiratory depression or failure	57 (11.6)	54 (11.1)	0.68
Life-threatening/lethal arrhythmia	86 (17.5)	85 (17.1)	0.89
Hypoxemia-pneumonia	56 (11.4)	57 (11.7)	0.34
Pulmonary embolism	19 (3.9)	18 (3.7)	0.66
Electrolyte disturbances	27 (5.5)	26 (5.3)	0.49
Other	7 (1.4)	6 (1.2)	0.75
Hospital admission cause, *n* (%)			
Acute cardiovascular disease	147 (29.9)	145 (29.8)	0.34
Acute respiratory disease	119 (24.2)	117 (24.1)	0.88
Acute neurologic disease	62 (12.6)	60 (12.3)	0.69
Acute digestive disease	69 (14.0)	68 (14.0)	0.87
Acute renal disease	40 (8.1)	40 (8.2)	0.81
Trauma	47 (9.6)	49 (10.1)	0.12
Other	8 (1.6)	7 (1.4)	0.26
Location of cardiac arrest, *n* (%)			
Ward	231 (47)	224 (46)	0.79
ICU or coronary care unit	138 (28)	141 (29)	0.74
Emergency department	98 (20)	92 (19)	0.70
Operating room	25 (5)	29 (6)	0.54

(*Continued*)

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TABLE 1. (*Continued*). Comparison of Demographic and Basal Clinical Characteristics of Patients Between Shenfu Injection and Control Groups

Characteristic	Shenfu Injection Group (*n* = 492)	Control Group (*n* = 486)	*p*
Initial cardiac rhythm, *n* (%)			
Ventricular fibrillation	51 (10.4)	49 (10.1)	0.65
Pulseless electrical activity	39 (7.9)	37 (7.6)	0.57
Asystole	402 (81.7)	400 (82.3)	0.78
ALS duration, median (IQR), min	13 (6–20)	19 (9–30)	0.27
No. of cardiopulmonary resuscitation cycles, median (IQR)	4 (2–6)	5 (3–8)	0.15
Time to ALS initiation, median (IQR), min	3 (1–4)	3 (1–4)	0.36

ALS = advanced life support, IQR = interquartile range.

The values are expressed as median (interquartile range, observations available) or *n* (%). Continuous variables were described as mean ± SD. Categorical variables are reported as frequencies and percentages. Comparisons between groups for categorical variables were made using the chi-square test. Comparisons of continuous variables between groups were carried out using the Mann-Whitney *U* test.

(HR, 0.55; 95% CI, 0.38–0.79; $p = 0.002$) compared with the control group. Other variables found to be significant in the Cox regression analysis of 28-day mortality were cause (non-cardiac vs cardiac; HR, 0.78; 95% CI, 0.34–0.95; $p = 0.02$), rhythm (VF/VT vs asystole/PEA; HR, 0.63; 95% CI, 0.46–0.91; $p = 0.03$), and hypothermia (use vs no use; HR, 0.72; 95% CI, 0.41–0.88; $p = 0.03$) (Table 3).

Protocol Adherence and Serious Adverse Events

Safety and tolerability of SFI were assessed by comparing all available information for the two groups with respect to detected outliers in laboratory safety data, drug-related serious adverse events (assessed by the investigator), and deterioration of organ and system function. Side effects were recorded when they occurred (e.g., tachycardia, rashes, dyspnea, dizziness, headaches, nausea and vomiting, and tremors). A side effect of pruritus was found in only two patients in the SFI group and was determined to not be related to the study drug. No interim dose adjustments were needed because of adverse effects, and one patient had an interrupted study protocol.

DISCUSSION

To the best of our knowledge, this was the first registered randomized, controlled trial to investigate the efficacy and safety of SFI for the treatment of patients after IHCA. Our findings indicated that combined use of SFI and PRCB treatment improved clinical outcomes in patients with ROSC after IHCA, including reduced 28-day and 90-day mortality rates compared with the conventional PRCB treatment alone. The data obtained from this study provide evidence that the inclusion of SFI therapy significantly improved hemodynamic, reduced damage to vital organs, and shortened both ventilation time and ICU stay.

The complex pathophysiological changes that occur after CA (PCAS) have a high-mortality rate and require a multidisciplinary approach as the optimal treatment (5). The SFI has been widely used in emergency departments and ICUs in China and shown to have beneficial effects on patients' rescue from sepsis (15). A meta-analysis of randomized controlled trials (RCTs) of SFI in septic shock patients had demonstrated that SFI could further increase MAP, normalize HR, clear blood lactate, and reduce mortality when compared with conventional therapy (9). Notably, SFI has been shown to be promising for the treatment of some clinical disorders including shock and ischemia/reperfusion injury of the brain, spinal cord, kidney, intestine, liver, and heart (15–20). Furthermore, more importantly, our previous animal studies also indicated that SFI mitigates postresuscitation myocardial dysfunction, lung injury, and cerebral injury and controls glycemia (19–21). These results suggest that compared with single PRCB treatment, SFI combined with PRCB treatment would be a more promising therapeutic strategy to offer favorable outcomes in PCAS patients.

There are few clinical studies about the molecular mechanisms of SFI in patients after CA, but some animal studies may provide clues about the mechanisms of SFI on the molecular level. For instance, Ji et al (22) found that SFI attenuated postresuscitation myocardial dysfunction by improving energy delivery and alleviation of oxygenation and lipid peroxidation. Mechanistically, SFI restores Na^+-K^+-ATPase and Ca^{2+}-ATPase activities, reduces malonaldehyde content and attenuates the decrease in superoxide dismutase activities in myocardial tissue, represses the opening of Ca^{2+} channels on the myocardial cell membrane, reduces the inflow of Ca^{2+}, inhibits calcium overload, affects PI3K/Akt signaling, and attenuates postresuscitation myocardial dysfunction by modulating apoptosis (23). SFI has also been shown to inhibit apoptosis in lung tissue and improve anti-lipid peroxidation after CA (24). In addition, a recent study demonstrated that SFI attenuated myocardial injury, regulated myocardial immune disorders, and protected against postresuscitation myocardial injury by modulating expression of transcription factors GATA-3 and T-bet (25). Zhang et al (26) examined the action of SFI in regulating the expression of the serum complements and inflammatory cytokines after ROSC and found that SFI attenuated postresuscitation immunodysfunction by modulating the expression of

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TABLE 2. Comparison of In-Hospital Treatment and Outcome in 28 d of Patients Between Two Groups

Variable	Shenfu Injection Group (*n* = 492)	Control Group (*n* = 486)	*p*
Comatose at ICU admission, *n* (%)	474 (96.3)	470 (96.7)	0.75
Ventilated, *n* (%)	488 (99.2)	481 (99.0)	0.67
Therapeutic hypothermia, *n* (%)	93 (18.9)	87 (17.9)	0.69
Angiography or percutaneous coronary intervention, *n* (%)	153 (31.1)	148 (30.5)	0.87
Morbidity/complication, *n* (%)			
Multiple organ failure	218 (44.3)	259 (53.3)	0.01
Renal failure	109 (22.1)	97 (20.2)	0.21
Acute respiratory distress syndrome	58 (11.7)	59 (12.1)	0.87
Cardiogenic shock, *n* (%)	50 (10.2)	54 (11.1)	0.91
Liver disease	14 (2.8)	5 (1.0)	0.32
Pancreatitis	13 (2.6)	6 (1.2)	0.36
Peritonitis	9 (1.8)	2 (0.4)	0.21
Fungemia	13 (2.6)	3 (0.6)	0.07
Other	8 (1.6)	1 (0.2)	0.12
Cause of death, *n* (%)			
Brain	183 (64.8)	231 (68.0)	0.88
Cardiac	54 (19.1)	75 (22.1)	0.79
Multiple organ failure	31 (10.9)	24 (7.0)	0.54
Other	14 (5.2)	10 (2.9)	0.43
Cerebral performance score at discharge, *n* (%)			
1or 2 (good cerebral performance to moderate cerebral disability)	143 (70.0)	83 (59.3)	0.03
3 (severe cerebral disability)	36 (17.7)	31 (22.1)	0.31
4 (coma or vegetative state)	24 (11.8)	26 (18.6)	0.04
Duration of mechanical ventilation (d), mean ± SD	8.6 ± 3.2	12.7 ± 7.9	< 0.001
Hospital stay (d), mean ± SD	8.7 ± 5.9	13.2 ± 8.1	< 0.001
Hospital cost (Renminbi Yuan), mean ± SD	59,520.7 ± 41,338.2	125,903.8 ± 64,475.7	< 0.001
28-day survival, *n* (%)	210 (42.7)	146 (30.1)	0.02
90-day survival, *n* (%)	195 (39.6)	126 (25.9)	0.001

The values are expressed as median (interquartile range [IQR], observations available) or *n* (%). Continuous variables were described as mean ± SD or median (IQRs) in the case of nonnormality of the distributions. Categorical variables are reported as frequencies and percentages. Comparisons between groups for categorical variables were made using the chi-square test. Comparisons of continuous variables between groups were carried out using the Mann-Whitney *U* test.

complements and cytokines levels. Given the abovementioned functions, this could, at least partly, explain that SFI could reduce the tissue damage during reperfusion and protected cellular structures via the above-referred multitarget effects to maintain organ function and prevent multiple organ dysfunction syndrome after CA. Consistent with these findings, our data further suggest that combined use of SFI and standardized PSCB treatment reduced the 28-day mortality in patients with ROSC after IHCA. In addition, SFI showed beneficial effects on secondary endpoints including an improved post-CA survival rate at 90 days, increased CPC scores at discharge, and shortened both ventilation time and ICU stay for PCAS patients.

Despite these advances, the safety of SFI has not been fully clinically verified. The reported occurrence rate adverse reactions to SFI is 0.87% (27). In our study, there was no increase in the reported morbidity in the SFI group. We consider SFI

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TABLE 3. Multivariate Cox Regression Analysis: Results of Stepwise Selection Procedure

Poor Outcomes (Event/Total Nos.)	Variable	Exp (B) = Hazard Ratio	95% CI for Exp (B)		*p*
			Lower	Upper	
28-day death (622/978)	Study center (overall)				0.75
	Group (SFI vs control)	0.61	0.43	0.89	0.009
	Cause (noncardiac vs cardiac)	0.78	0.34	0.95	0.02
	Rhythm (VF/VT vs asystole/PEA)	0.63	0.46	0.91	0.03
	Hypothermia (use vs no use)	0.72	0.41	0.88	0.03
90-day death (757/978)	Study center (overall)				0.67
	Group (SFI vs control)	0.55	0.38	0.79	0.002
	Cause (noncardiac vs cardiac)	0.67	0.42	0.84	0.01
	Rhythm (VF/VT vs asystole/PEA)	0.61	0.39	0.90	0.006
	Hypothermia (use vs no use)	0.75	0.44	0.96	0.04

EXP = exponent, PEA = pulseless electrical activity, SFI = Shenfu injection, VF/VT = ventricular fibrillation/pulseless ventricular tachycardia.

A Cox proportional hazards regression model was applied to determine the independent contribution of variables to the prediction of 28-day and 90-day death. The Cox regression model were adjusted for age, gender, study center (overall), group (SFI vs control), cause (cardiac vs noncardiac), rhythm (VF/VT vs asystole/PEA), hypothermia (use vs no use), and epinephrine dose (mg) during cardiopulmonary resuscitation.

to be a relatively safe drug although a large-scale prospective study should be performed to further corroborate our evaluation.

LIMITATIONS

The current clinical trial had several limitations. First, the study population was heterogeneous with respect to clinical features. In fact, unbalanced baseline characteristics between groups are not rare in CA trials even with large cohorts. In our study, to assess whether outcomes differed by treatment groups, linear mixed models for longitudinal data were fitted with adjustment for the baseline value. This method has been widely used in multicenter research (28). Second, our study was an assessor-blinded RCT, and because the SFI is yellow in color, it was impossible to blind the physicians to the treatment assignment. We are planning to design a double-blinded RCT in the next stage. Third, since a considerable proportion of patients were transferred out of the ICU within 1 week (many patients were unable to continue treatment in the ICU because of the high cost of hospitalization and many others abandoned treatment), it was difficult to obtain complete laboratory and follow-up data. We therefore only collected laboratory data within 14 days and followed up regarding survival status for 90 days. A more extensive laboratory data collection and extended follow-up period could possibly provide more insight. Fourth, therapeutic hypothermia was used in very few ICUs in our study, with only 18.4% of patients (180/978) receiving therapeutic hypothermia. Fifth, side effects are one of the main concerns regarding herbal medication. Although we did not observe any severe side effects related to SFI treatment, to be more cautious, additional clinical studies are needed to further explore the potential side effects of SFI treatment in a broader manner. Finally, our study was not powered to make a reliable assessment of 1-year outcomes.

CONCLUSIONS

In conclusion, this prospective, multicenter, randomized, controlled study demonstrates that SFI in combination with conventional PRCB treatment is effective for improving clinical outcomes in patients with ROSC after IHCA. We found that a 14-day treatment with IV administration of SFI in these patients was associated with increased 28-day and 90-day survival rates, increased CPC scores at discharge, shortened ventilation time, and shortened ICU stay. A larger randomized controlled study with SFI is needed to further corroborate the survival benefits observed in our study and to investigate potential mechanisms underlying these benefits.

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