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Protective Effect of Shenqi Fuzheng Injection on Myocardial Depression with Septic Shock

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Abstract

Objective: This study aimed to evaluate whether Shenqi Fuzheng injection (SFI) could improve sepsis-induced myocardial depression (SIMD) in patients with septic shock.

Methods: A total of 361 patients who were admitted into the intensive care unit at the First Affiliated Hospital of Dalian Medical University between January 2012 and December 2017 were included in the study. All patients met the Sepsis 3.0 diagnostic criteria and were classified into an SFI group and a non-SFI group. The hemodynamic parameters, cardiac biochemical markers, echocardiography, Acute physiology and chronic health evaluation II (APCHE II) scores, sequential organ function assessment (SOFA) and prognosis were compared between the groups 12, and 24 and 72 hours after receiving treatment.

Results: SOFA and cardiac related markers, including brain natriuretic peptide (BNP), creatine kinase (CK) and CK-muscle/brain (MB) were significantly lower in the SFI group than in the non-SFI group ($P < 0.05$). Left ventricular ejection fraction (LVEF), left ventricular end diastolic volume (LVEDV) and lactate were significantly decreased in patients treated with SFI compared to those with non-SFI. SFI shortened the duration of ICU stay and improved 28-day survival ($P < 0.05$).

Conclusion: SFI improves the survival of patients with septic shock by improving SIMD and microcirculation.

Keywords: *Septic Shock; Sepsis-Induced Myocardial Depression; Shenqi Fuzheng Injection (SFI); Fluid Resuscitation*

Abbreviations

SIMD: Sepsis-Induced Myocardial Depression; SFI: Shenqi Fuzheng Injection; SOFA: Sequential Organ Function Assessment; BNP: Brain Natriuretic Peptide; CK: Creatine Kinase; CK-MB: CK-Muscle/Brain; SSVRI: Stroke Systemic Vascular Resistance Index; PP: Pulse Pressure; SVI: Stroke Volume Index; **ICU**: Intensive Care Unit; SVR: Peripheral Vascular Resistance; TCM: Traditional Chinese Medicine; EICU: Emergency Intensive Care Unit; MAP: Mean Arterial Pressure; IABP: Intra-Aortic Balloon Pump; EGDT: Early Goal-Directed Therapy; CVP: Central Venous Pressure; PiCCO: Pulse Indicator Continuous Cardiac Output; CO: Cardiac Output; PCCO: Pulse Contour Cardiac Output; HR: Heart Rate; RR: Respiratory Rate; SPO_2: Blood Oxygen Saturation; CI: Cardiac Index; EVLWI: Extravascular Lung Water Index; SVRI: Systemic Vascular Resistance Index; PVPI: Pulmonary Vascular Permeability Index; SSVRI: Stroke Systemic Vascular Resistance Index; Tni: Troponin I

Background

Sepsis shock, defined as a persistent demand for vasoactive drugs, despite adequate fluid resuscitation, to maintain the level of mean arterial pressure (> 65 mmHg) and blood lactate (> 2 mMol/L), is a critical illness with a dismal prognosis [1]. Sepsis-induced myocardial depression (SIMD) is a common complication in patients with septic shock. This complication is associated with an increased risk of mortality. SIMD is a reversible myocardial depression, which is characterized by systolic and diastolic dysfunction and decreased ejection fraction [2]. The incidence of SIMD was reported at 18~65%, corresponding to a mortality rate as high as 40~70% [3].

The pathogenesis of SIMD involves multiple mechanisms, including circulating myocardial inhibitors (such as bacterial toxins, cytokines and complement systems), myocardial factors (such as mitochondrial damage, oxidative stress, apoptosis, nitric oxide production and calcium homeostasis) and autonomic dysfunction [4]. In addition, the peripheral vascular resistance (SVR) and changes in right ventricular function also play a role in the development of SIMD. Previous studies investigating septic shock have demonstrated a positive relationship between SVR and survival rate. Those who survived from septic shock had a remarkably higher level of SVR compared to the levels observed in non-survivors [2].

Shenqi Fuzheng injection (SFI) is a well-known traditional Chinese medicine (TCM) that is concocted from two kinds of herbs: Radix Astragali (root of astragalus; Chinese name: Huangqi) and Radix Codonopsis (root of *Codonopsis pilosula*; Chinese name: dangshen). SFI has been declared to reverse multiple organ injury, boost immunity and curb tumor growth [5-7]. However, the effect of SFI on SIMD has not been discovered so far. In this clinical study, we attempted to investigate whether SFI would ameliorate SIMD and improve the prognosis.

Materials and Methods

Patients and study design

Patients who were diagnosed with septic shock and admitted into the emergency intensive care unit (EICU) at the First Affiliated hospital of Dalian Medical University between January 2012 and December 2017 were eligible for the study. The study was approved by the ethics committee of the hospital (YJ-KY-FB-20). All patients or their guardians signed the informed consent.

The inclusion criteria included: 1) adult patient (aged 18~80 years); 2) meeting the Sepsis 3.0 diagnostic criteria, specifically with infection, sequential organ failure score (SOFA) ≥ 2 points, a MAP < 65 mmHg after fluid resuscitation, a requirement for vasoconstrictor drugs to maintain blood pressure, and an arterial lactate value greater than 2 mmol/L; 3) receiving active treatment immediately after admission with a life expectancy over 72h; 4) informed consent signed.

The exclusion criteria were as follows: 1) accompanied with serious underlying diseases or conditions such as acute myocardial infarction, severe cardiac insufficiency, malignant arrhythmia such as ventricular tachycardia or ventricular fibrillation, receiving intra-aortic balloon pump (IABP), severe bleeding disorders, malignant tumors, liver or kidney failure, severe cerebrovascular disease, such as brain stem hemorrhage; 2) suspected infection at the puncture site; 3) pregnancy; 4) heparin allergy; 5) died within 72 hours following admission or refused treatment.

A total of 361 cases were ultimately included. The sites of infection were as follows: abdominal (n = 108), pulmonary (n = 138), biliary (n = 36), urinary (n = 43), soft tissue (n = 10) and others (n = 26; Table).

All of the included patients were randomly classified into two groups: an SFI group and a non-SFI group. SFI was administered at 250 ml once daily for 7 consecutive days. Early goal-directed therapy (EGDT) and fluid resuscitation was applied. Treatment of mechanical

ventilation, sedation, anti-infective treatment, and nutritional support was applied. The target of fluid resuscitation was: central venous pressure (CVP) ≥ 8 - 12 mmHg, mean arterial pressure (MAP) ≥ 65 mmHg, urine volume ≥ 0.5 ml/(kg·h), Central venous oxygen saturation ($ScvO_2$) ≥ 70%, mental status and skin temperature recovered, no spots.

Measurements and data collection

Systemic hemodynamic parameters were measured by pulse indicator continuous cardiac output (PiCCO; Intelli Vue MP60, Phillips, Germany). Central venous access was established through insertion of subclavian vein for cold water injection and CVP measurement. A thermistor-tipped arterial catheter (4F, PV2014L16, PUSION, Germany) was placed into the femoral artery. The patient information, including height, weight, and other basic items was obtained from the monitoring system to input. When a stable baseline was obtained, a cold saline solution (< 5°C) was injected as quickly as possible and repeated three times, the PiCCO monitoring value was then calculated (the measured value is the thermodilution measurement instantly pulse indicator continuous cardiac output (CO), after which the monitor displays the CO value named the pulse contour cardiac output (PCCO).

Indicators of MAP, heart rate (HR), blood oxygen saturation (SPO_2), respiratory rate (RR) and urine volume were monitored to guide early goal-directed therapy (EGDT) and fluid resuscitation. Cardiac index (CI), Stroke volume index (SVI), systemic vascular resistance index (SVRI), extravascular lung water index (EVLWI), pulmonary vascular permeability index (PVPI), stroke systemic vascular resistance index (SSVRI) and pulse pressure/stroke volume index (PP/SVI), as a marker of arterial stiffness, were measured to quantify the changes in fluid volume and velocity.

All systemic hemodynamic parameters were collected at admission, as well as 12, 24 and 72 hours, 7days and 10 days after admission. Blood was withdrawn for the measurement of lactate, creatine kinase (CK), CK-isoenzyme (CK-Mb), troponin I (TnI) and brain natriuretic peptide (BNP). The lactate clearance rate and 28-day mortality was recorded.

Left ventricular ejection fraction (LVEF) and left ventricular end diastolic volume were collected on the 1^{st}, 7^{th}, 10^{th} days after admission by bedside ultrasound (LOG7QeR7, GM, USA).

Statistical analysis

Categorical variables are expressed as numbers and percentages and were analyzed by chi-square test or Fisher's exact test. Continuous variables are presented as mean ± standard deviation (x ± s) and independent t-tests were used for between group comparisons. The correlation was calculated by the spearman correlation. $P < 0.05$ was considered to be statistically significant. All data were analyzed by SPSS 22.0 software.

Results

Demographic and baseline characteristics

A total of 361 patients were included in the study. Among them, 152 (42.1%) were male with an average age of 50 (range 28 - 73) years. There were 209 (57.9%) female patients and, within this group, the average age was 52 (range 22 - 70) years. No significant difference in the baseline characteristics was found between the SFI and non-SFI groups (Table 1). The infection sites and infectious organisms are displayed in table 2.

Group	SFI group	Non - SFI group	P value
Age	51 (28 - 70) 52 (22 - 65)	50 (30 - 73) 51 (25 - 70)	0.966
Male/female	80/105	72/104	0.754
MAP (mmHg)	55 (42 - 59)	53 (45 - 57)	0.921
PCT (ng/ml)	29 (5 - 100)	30 (7 - 100)	0.527
SOFA score	12 (6 - 20)	13 (5 - 22)	0.653
CK (U/L)	240 (165 - 385)	284 (186 - 360)	0.217
CK - Mb (ug/L)	26 (10 - 46)	22 (8 - 40)	0.785
TnI (ug/L)	1.29 (0.3 - 5.6)	1.98 (0.6 - 6.3)	0.342
BNP (pg/ml)	1890 (350 - 2780)	1754 (460 - 2265)	0.829
HR (bpm)	116 (98 - 130)	119 (100 - 142)	0.736
Lac (mmol/L)	6.5 (3.9 - 12)	5.9 (4.2 - 10)	0.463

Table 1: *Demographic and baseline characteristics in SFI and non-SFI groups.*

Date were expressed as median (range) or number (%) as appropriate.

MAP: Mean Arterial Pressure, PCT: Procalcitonin, SOFA: Sequential Organ Function Assessment, CK: Creatine Kinase, CK-Mb: CK-Muscle/Brain, TnI: Troponin I, BNP: Brain Natriuretic Peptide, HR: Heart Rate, Lac: Lactate.

	SFI group (n = 185)	Non-SFI group (n = 176)
Infection site		
Respiratory	75	63
Abdominal		
IAI	50	58
IBT	20	16
Urinary		
Pyelonephritis (rhabdomyolysis and acute renal failure)	23	20
Others		
Trauma	7	10
CRBI	4	5
Skin/soft tissues	6	4
Infectious organism (%)		
Gram negative	57.27	47.62
Gram positive	27.7	36.9
Fungal	9.3	11.43
Viral	5.73	4.05

Table 2: *Characteristics of patients in the SFI and non-SFI groups.*

IAI: Intra-Abdominal Infection; IBT: Infection of Biliary Tract, CRBI: Catheter-Related Infection.

Comparison of hemodynamic parameters

At 24 hrs after treatment was commenced, the hemodynamic indicators of MAP, SSVRI and PP/SVI were significantly higher in the SFI group than in the non-SFI group. A similar pattern was observed in the urine output. However, the EVLWI was significantly lower in the SFI group than in the non-SFI group. Additional parameters, including CI, SVI, MAP, CVP, PP, PVPI and SVRI, did not differ between the two groups (Table 3).

Group	SFI group	Non-SFI group	P value
CI (L/min/m^2)	3.00 ± 0.29	3.26 ± 0.27	0.115
SVI (L/min/m^2)	31.0 ± 1.71	32.9 ± 2.19	0.097
HR (bpm)	108.67 ± 10.04	98.8 ± 15.2	0.167
MAP (mmHg)	69.2 ± 1.09	70 ± 1.58	0.30
CVP (cmH_2O)	7.67 ± 0.79	8.5 ± 0.61	0.065
PP (mmHg)	64.89 ± 1.76	63.2 ± 1.48	0.09
SVRI (dynes·sec/cm^5/m^2)	1693.1 ± 48.22	1658 ± 52.63	0.23
EVLW (ml/kg)	6.33 ± 1.48	11.7 ± 4.37	0.004
PVPI (%)	3.56 ± 1.21	3.78 ± 1.58	0.08
SSVRI (mmHg/ml/m^2)	159.13 ± 7.3	149.92 ± 7.28	0.043
PP/SVI (mmHg/ml/m^2)	2.09 ± 0.15	1.60 ± 0.12	0.004
0 h SOFA	12.89 ± 1.27	13.2 ± 2.28	0.504
24 h SOFA	6.0 ± 1.12	8.4 ± 2.61	0.031
24 h Lactate clearance rate (%)	60.8 ± 3.64	55.88 ± 2.34	0.018
Duration of ventilation (hr)	87.41 ± 9.37	101.26 ± 11.56	<0.05
Length of ICU stay (d)	9.87 ± 1.34	13.51 ± 3.21	<0.05
Success rate of fluid resuscitation (%)	83 (66/81)	60 (38/71)	<0.05
28-day mortality	23.5 (19/81)	46.5 (33/71)	<0.05

Table 3: *Comparisons of hemodynamic parameters, SOFA score and biochemical biomarkers between the groups. CI: Cardiac Index; SVI: Stroke Volume Index; HR: Heart Rate; MAP: Mean Arterial Pressure; CVP: Central Venous Pressure; PP: Pulse Pressure; SVRI: Systemic Vascular Resistance Index; EVLW: Extravascular Lung Water; PVPI: Pulmonary Vascular Permeability Index; SSVRI: Stroke Systemic Vascular Resistance Index; PP/SVI: Pulse Pressure/Stroke Volume Index; SOFA: Sequential Organ Function Assessment.*

Comparison of biochemical biomarkers

The baseline parameters, including HR, MAP, LAC, SOFA score, urine volume, BNP, CK, CK-Mb, and TnI, did not differ between the SFI and non-SFI groups ($P > 0.05$). At 12 hrs, the level of TnI was significantly lower in the SFI group than in the non-SFI group ($P < 0.05$). At 24 hrs, a significantly improvement in the BNP, CK, CK-Mb, TnI measurements and SOFA score were observed in the SFI group ($P < 0.05$ at both 24 hrs and 72 hrs). The lactate level was lower in the SFI group than in the non-SFI group at 24 hrs ($P < 0.05$). However, this difference was no longer significant at 72 hrs. Measurements of HR, urine output and MAP were markedly higher in the SFI group than in the non-SFI group at 72 hrs ($P < 0.05$; Figure 1).

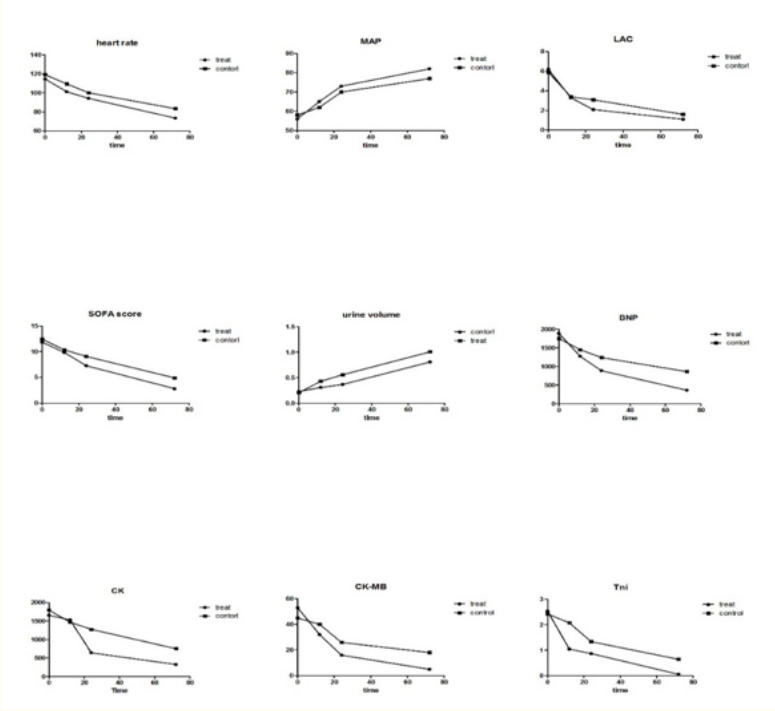

Figure 1: *Differences in hemodynamic and biochemical parameters between the groups.*

Comparison of prognosis

The duration of mechanical ventilation in the SFI and non-SFI groups was 87.41 ± 9.37 and 101.26 ± 11.56 hrs, respectively. This between-group difference was significant ($P < 0.05$). The length of the ICU stay was significantly shorter in the SFI group than in the non-SFI group (9.87 ± 1.34 vs 13.51 ± 3.21 days, $P < 0.05$). The success rate of fluid resuscitation and the survival rate were significantly higher in the SFI group than in the non-SFI group (83% vs 60%, $P < 0.05$, table 3).

Comparison of cardiac function parameter

The levels of LVEF and LEDV did not differ between SFI and non-SFI group at 1 days ($p > 0.05$, table). At 7 days and 10 days, the levels of LVEF and LEDV were significantly different from 1 days between SFI and non-SFI groups ($p < 0.05$).

Relationship between 28-day mortality and vascular elasticity-related markers

The levels of BNP, TnI, CK-MB were all positively correlated with 28-day mortality. The correlation coefficient with mortality was 0.814 for BNP, 0.656 for CK-MB and 0.540 for TnI (all $P < 0.05$; Figure 2). A significant negative correlation was observed between 28-day mortality and vascular elasticity-related markers including PP/SVI and SSVRI (Figure 3).

Correlations			
		28 days survival	BNP
28 days survival	Pearson Correlation	1	-.814**
	Sig. (2-tailed)		.000
	N	72	72
BNP	Pearson Correlation	-.814**	1
	Sig. (2-tailed)	.000	
	N	72	72
**. Correlation is significant at the 0.01 level (2-tailed).			
Correlations			
		28 days survival	**Tn-i**
28 days survival	Pearson Correlation	1	-.540**
	Sig. (2-tailed)		.000
	N	72	72
Tn-i	Pearson Correlation	-.540**	1
	Sig. (2-tailed)	.000	
	N	72	72
**. Correlation is significant at the 0.01 level (2-tailed).			
Correlations			
		28 days survival	**CK-MB**
28 days survival	Pearson Correlation	1	-.656**
	Sig. (2-tailed)		.000
	N	72	72
CK-MB	Pearson Correlation	-.656**	1
	Sig. (2-tailed)	.000	
	N	72	72

Figure 2: *Correlations between BNP, TnI, CK-MB and 28-day mortality.*

Correlations			
		28 days mortality	PP/SVI
28 days mortality	Pearson Correlation	1	-.984**
	Sig. (2-tailed)		.000
	N	31	31
PP/SVI	Pearson Correlation	-.984**	1
	Sig. (2-tailed)	.000	
	N	31	31
**. Correlation is significant at the 0.01 level (2-tailed).			
Correlations			
		28 days mortality	**SSVRI**
28 days mortality	Pearson Correlation	1	-.889**
	Sig. (2-tailed)		.000
	N	31	31
SSVRI	Pearson Correlation	-.889**	1
	Sig. (2-tailed)	.000	
	N	31	31
**. Correlation is significant at the 0.01 level (2-tailed).			

Figure 3: *Correlations between PP/SVI, SSVRI and 28-day mortality.*

The heart rate, mean arterial pressure (MAP), lactate (LAC), sequential organ function assessment (SOFA) score, urine volume, brain natriuretic peptide (BNP), creatine kinase (CK), CK-muscle/brain (CK-MB), and troponin I (TnI) measurements in both groups. The level of Lac, the SOFA score, and the CK, CK-MB, BNP and TnI levels were considerably lower in the SFI group than in the non-SFI group (Figure 1).

Discussion

Sepsis is a deleterious systemic host response to infection or injury that leads to a high rate of morbidity and mortality in ICUs [1,8]. SIMD is common in patients with septic shock but our understanding of this condition is still lacking. The current study showed that the parameters that reflect the peripheral vascular status were impaired in this condition while the macro hemodynamic indicators, such as CI, remained within the normal range. SFI effectively reversed the changes of SIMD and reduced the mortality rate by improving the changes to the vascular elasticity index, and myocardial and tissue perfusion-related markers.

Microvascular disturbance plays a pivotal role in sepsis-related mortality. The sepsis-induced damage to the microvasculature increases the permeability of the endothelial membrane, which results in capillary leakage and abnormalities in microcirculatory flow. SIMD may occur at the initial stage of septic shock. However, the normal range of indicators, such as cardiac output, may be maintained, due to the increased ventricular volume and decreased peripheral vascular resistance [9]. In the current study, we found that cardiac output was approximately normal in both of the studied groups while the level of TnI, CK, CK-MB was significantly impaired at the early stage of septic shock, which confirmed the abovementioned concept. The parameters that reflected the extent of myocardial injury showed peaks at 12 hrs after the onset of sepsis [10]. We observed a significant improvement in the levels of TnI, CK-MB, CK after the treatment of SFI, demonstrating a cardiac protective effect of SFI.

Sepsis induced microvascular disturbance is mediated by multiple inflammatory cytokines and endotoxins. Animal studies have revealed that cytokines, including TNF, IL-1β and IL-6, participate in the pathogenesis of SIMD. SIMD is relieved by suppressing the expression of these inflammatory cytokines [10,11]. Some studies have demonstrated that inflammatory cytokines are released from neutrophils, monocytes, macrophages and endothelial cells at the early stage of sepsis, leading to cardiomyocyte apoptosis and cardiac dysfunction [12,13]. Although we did not measure the changes in the expression of inflammatory cytokines following septic shock, our results show that the level of BNP was markedly lower in the SFI group than in the non-SFI group. This indicates that SFI improved myocardial dysfunction [14].

Tissue hypoxia, caused by disordered microcirculation, is a major factor in sepsis [15-17]. Lactate is a marker of tissue perfusion and is associated with the outcome in patients with sepsis or septic shock [18]. In this study, we observed that SFI improved the microcirculation by boosting the clearance of lactate. Another important factor that is associated with the prognosis of septic patients is the changes in peripheral vascular tone that are reflected in SVRI, SSVRI and PP/SVI, as shown in the current study. After receiving SFI, patients with septic shock had an improved 28-day survival rate.

Previous animal studies have demonstrated that SFI has a protective effect on myocardial ischemia-reperfusion injury in mice. SFI inhibits the apoptosis of cardiomyocytes by downregulating the expression of Bax and upregulating the expression of Bcl-2. We further demonstrated that SFI could improve SIMD through mechanisms that involve microcirculation and cardiomyocytes. The application of SFI obviously reduced the duration for which ventilation was required and the ICU stay, increased the success rate of fluid resuscitation and improved the 28-day survival rate in patients with septic shock.

There are several limitations in this study. The sample size is small and the application of PiCCO was limited by its invasiveness. A large prospective trial is certainly necessary to verify the effectiveness of SFI and to explore the underlying mechanisms involved in its role in septic shock.

Conclusion

SFI improves the survival of patients with septic shock by improving SIMD and microcirculation.

Ethics Approval and Consent to Participate

The above named research has been granted ethical approval by the Ethics Committee of First Affiliated Hospital of Dalian Medical University for submitting a research paper for publication.

Consent for Publication

Not applicable.

Availability of Data and Materials

Please contact author for data requests.

Funding

None.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

Zhiqin Kang carried out data collection, and statistics. Li Jiang carried out the design of the study and coordination and helped to draft the manuscript.

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