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Clinical Experience

Effect of Shen-Fu Injection (参附注射液) on Hemodynamics in Early Volume Resuscitation Treated Septic Shock Patients*

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ABSTRACT **Objective:** To investigate the hemodynamic effect of Shen-Fu Injection (参附注射液, SFI) in early volume resuscitation treated septic shock patients by monitoring pulse indicator continuous cardiac output (PICCO). **Methods:** All septic shock patients admitted in the Intensive Care Unit of the Affiliated Hospital of Shandong University of Traditional Chinese Medicine from January 1st, 2014 to December 31th, 2015, were reviewed, and totally 65 were enrolled in this study. They were assigned to SFI group (33 cases) and control group (32 cases). All 65 patients underwent conventional treatment mainly including volume resuscitation, antibiotics and vasoactive drugs therapy. The patients of the SFI group received additional 100 mL of SFI intravenously every 12 h. In all 65 patients, the PICCO arterial catheter and vein catheter were implanted within 1 h after the diagnosis of septic shock. In the course of early volume resuscitation, hemodynamic data of patients were recorded by PICCO monitor at 0, 12, and 24 h after the catheter implantation. **Results:** The hemodynamic indices of the two groups showed no significant differences at the beginning of 0 h (P>0.05). At 12 and 24 h, the hemodynamic indices of SFI group were significantly improved in comparison with the control group (P<0.05), including cardiac index (CI), global end diastolic volume index (GEDI), mean arterial pressure (MAP) and heart rate (HR). In addition, there was no significant change of extra-vascular lung water index between the two groups (P>0.05). **Conclusion:** SFI significantly improved hemodynamic indices such as CI, GEDI, MAP and HR in early volume resuscitation treated septic shock patients.

KEYWORDS septic shock, hemodynamic, Shen-Fu Injection, Chinese medicine, pulse indicator continuous cardiac output

With the development of survival sepsis compaign (SSC) and the application of sepsis management guidelines, the treatment of sepsis and septic shock become more and more standardized. Nevertheless, the morbidity and mortality is still high in sepsis and septic shock patients.

Shen-Fu Injection (参附注射液, SFI) extracted from Chinese medicine (CM) *Radix Ginseng Rubra* and *Radix Aconiti Lateralis Preparata*, this formula has been used in clinic for over 2,000 years in treating cardiac diseases such as coronary heart disease, myocardial ischemia and heart failure in China, Korea and Japan.

The major active ingredients of red ginseng are ginsenosides also known as triterpene glycosides. Modern pharmacological research shows that ginsenosides confer beneficial effects on cardiovascular system through various mechanisms such as adjusting blood pressure, modifying vasomotor function, and influencing ion channels.[1-3] The major active ingredient of aconite is higenamine (HG) that has positive inotropic and chronotropic action in the heart.[4,5] Moreover, HG plays a protective role in myocardial cells, being responsible for

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improvement of hemodynamics. HG can improve coronary circulation, and thus decrease the injury of acute myocardial ischemia.

As a well-known CM, SFI has been widely used in clinic showing a curative effect during shock and resuscitation. Previous study shows that SFI can improve microcirculation, aiding in an inflammatory reaction and protecting ischemic myocardial cell.[6] Additionally, SFI enhances heart contractility and improves coronary circulation that helps elevate blood pressure and improve hemodynamics. Therefore, SFI may have a great potential in treating septic shock though lack of supporting data from evidence-based medicine. The current clinical trial has been designed to investigate the effect of SFI on hemodynamics in early volume resuscitation treated septic shock patients by monitoring pulse indicator continuous cardiac output (PICCO).

METHODS

Diagnostic, Inclusion and Exclusion Criteria

The international consensus definition of septic shock was used according to 2012 SSC guidelines for management of severe sepsis and septic shock.[7] The diagnostic criteria consists of a serious infection plus two or more systemic inflammatory response syndrome (SIRS) and shock criteria. The presence (probable or documented) of infection, SIRS criteria include: (1) heart rate >90 beats/min, (2) body temperature >38.3 ℃ or <36 ℃, (3) tachypnea (>20 breaths/min) or PCO_2 >32 mm Hg, and (4) leukocytosis [white blood cell (WBC) $>12.0\times10^9$/L, or 4.0×10^9/L or >10% bands]; persisting sepsis-induced hypotension (hypotension, elevated lactate, or oliguria) despite adequate fluid resuscitation; with organ failure.

Inclusion criteria include: (1) patients should meet the diagnostic criteria for septic shock; (2) aged 18–80 years old; (3) onset time within 24 h; (4) patients should be hospitalized.

Exclusion criteria include: (1) patients combined with diseases that may affect monitoring data of PICCO, such as intra-cardiac shunt, aortic aneurysm, aortic stenosis, and pulmonary lobectomy; (2) patients combined with other diseases that may affect lactic acid level, such as diabetic ketoacidosis and severe liver disease; and (3) patients presented other cause of shock, such as cardiac shock, neurogenic shock, and allergic shock.

Study Design

All septic shock patients admitted in the Intensive Care Unit (ICU) of the Affiliated Hospital of Shandong University of Traditional Chinese Medicine were reviewed from January 1st, 2014 to December 31th, 2015, and totally 65 septic shock patients were enrolled. They were assigned to SFI group (conventional therapy + SFI, 33 cases) and control group (conventional therapy alone, 32 cases). All patients underwent conventional treatment mainly including the volume resuscitation, antibiotics and vasoactive drugs according to 2012 SSC International Guidelines for Management of Severe Sepsis and Septic Shock.[7] The SFI group underwent conventional therapy plus SFI (10 mL per piece, Ya'an San-jiu Pharmaceutical Co., Ltd., Sichuan Province, China; batch No.130903010) 100 mL intravenous drip every 12 h SFI was administered within 1 h after septic shock diagnosis.

In all 65 patients enrolled in this study, the PICCO arterial catheter and vein catheter were implanted within 1 h after the diagnosis of septic shock. In the course of early volume resuscitation, hemodynamic data of patients were monitored by PICCO monitor at 0, 12, 24 h after the catheter implantation. The hemodynamic and blood gas data were analyzed and compared to investigate the effects of SFI on hemodynamics in early volume resuscitation treated septic shock patients. Hemodynamic data include cardiac index (CI), global end diastolic volume index (GEDI), extra-vascular lung water index (ELWI), mean arterial pressure (MAP) and heart rate (HR).

Resuscitation Goals

The initial resuscitation goals of all the enrolled patients should meet the following criteria during the first 6 h of resuscitation according to the strategy of early goal-directed therapy: (1) central venous pressure 8–12 mm Hg, (2) MAP ⩾65 mm Hg, (3) urine output ⩾0.5 mL·kg·h, and (4) superior vena cava oxygenation saturation ($Scvo_2$) or mixed venous oxygen saturation (Svo_2) 70% or 65%, respectively.

Statistical Analysis

Statistical analysis was performed using the SPSS 17.0 software (SPSS, Inc., Chicago, IL, USA) via a normal distribution test (Kolmogorov Smirnov test) and homogeneity test for variance (Levene's *t*-test). The data are presented as the mean ± standard deviation ($\bar{x}\pm s$). Statistical differences

between the two groups were assessed using independent-samples *t* test. Differences at different time points within the same group were compared using paired-samples *t* test. pH value and BE level were analyzed using non-parametric test. $P<0.05$ was considered to have a significant difference.

RESULTS

Comparison of Baseline Characteristics between Groups

The general conditions of the septic shock patients on admission showed no differences between two groups ($P>0.05$, Table 1).

Table 1. Baseline Characteristics of Septic Shock Patients on Admission

Variable	SFI group (33 cases)	Control group (32 cases)
Ages (Year, $\bar{x}\pm s$)	66.27 ± 5.70	66.47 ± 5.38
Male/female (Case)	25/8	23/9
Cause of sepsis [case (%)]		
Pulmonary infection	16 (48.5)	15 (46.9)
Abdominal infection	7 (21.2)	5 (15.6)
Multiple trauma	5 (15.1)	7 (21.9)
Catheter related blood stream infection	3 (9.1)	2 (6.2)
Others	2 (6.1)	3 (9.4)
Organ failure conditions [Case (%)]		
1–2	26 (78.8)	22 (68.8)
3 or more	7 (21.2)	10 (31.2)
Intercurrent conditions (Score)		
APACHE Ⅱ	19.45 ± 3.19	18.72 ± 3.05
SOFA	9.36 ± 2.90	8.81 ± 3.20
Fluid infusion volume within 24 h (mL)	3384 ± 324	3208 ± 295
Dosage of norepinephrine within 24 h ($ug\bullet kg^{-1}\bullet min^{-1}$)	0.21 ± 0.06	0.25 ± 0.05

Notes: APACHE Ⅱ: acute physiology and chronic health evaluation; SOFA: sequential organ failure assessment

Effect of SFI on CI, GEDI and ELWI in Septic Shock Patients

Before treatment (0 h), CI and GEDI of patients in both groups showed no obvious difference ($P>0.05$). After treatment, CI and GEDI of both SFI and control groups increased significantly at 12 and 24 h ($P<0.05$). Although CI and GEDI were improved in both groups, the increase of CI and GEDI in SFI group was significantly higher than that in the control group at either 12 or 24 h ($P<0.05$, Figure 1).

At different time point, ELWI showed no significant difference ($P>0.05$) between the two groups. Even within the same group, there was no significant change of ELWI among different time points ($P>0.05$, Figure 1).

Effect of SFI on MAP and HR in Septic Shock Patients

There was no statistical difference of patients' MAP and HR between SFI and control groups at 0 h ($P>0.05$). After treatment, MAP was increased and HR decreased significantly at 12 and 24 h in both groups ($P<0.05$). Compared with the control group, the change of MAP and HR in the SFI group was significantly greater at 12 and 24 h ($P<0.05$, Table 2).

Table 2. Comparison of Hemodynamic Data in Septic Shock Patients between Groups ($\bar{x}\pm s$)

Group	Case	Time	MAP (mm Hg)	HR (beats/min)
SFI	33	0 h	61.22 ± 3.31	119.55 ± 12.00
		12 h	73.45 ± 5.09*△	97.36 ± 6.55*△
		24 h	81.65 ± 4.30*△	76.52 ± 5.84*△
Control	32	0 h	59.81 ± 3.89	120.25 ± 12.04
		12 h	70.22 ± 4.00*	106.91 ± 5.94*
		24 h	79.12 ± 4.42*	84.75 ± 10.53*

Notes: *$P<0.05$ *vs*. 0 h in the same group; △$P<0.05$ *vs*. control group at the same time point

Comparison of Blood Gas Analysis Data between Groups

Before the treatment (0 h), blood gas indices including lactic acid, pH and BE showed no significant difference between SFI and control groups ($P>0.05$).

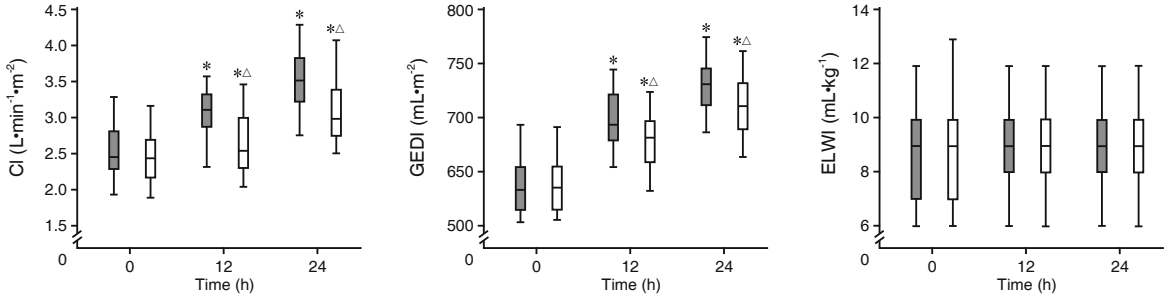

Figure 1. Comparison of CI, GEDI and ELWI Changes in Septic Shock Patients between Groups ($\bar{x}\pm s$)
Notes: *$P<0.05$ *vs*. 0 h in the same group; △$P<0.05$ *vs*. control group at the same time point

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After treatment, the three blood gas indices all improved in both groups at 12 h, particularly at 24 h (P<0.05). Compared with the control group, the change of the three blood gas indices in the SFI group was obviously greater at both 12 and 24 h (P<0.05, Table 3).

Table 3. Comparison of Blood Gas Indices in Septic Shock Patients between Groups ($\bar{x} \pm s$)

Group	Case	Time	Lactic acid (mmol/L)	pH	BE (mmol/L)
SFI	33	0 h	7.14±1.49	7.22±0.27	–7.93±1.25
		12 h	5.27±1.16*△	7.34±0.19*△	–5.27±1.60*△
		24 h	2.92±0.90*△	7.36±0.18*△	–3.26±0.75*△
Control	32	0 h	7.13±1.62	7.21±0.36	–7.92±1.24
		12 h	6.01±1.30*	7.31±0.26*	–6.08±1.40*
		24 h	3.48±0.99*	7.35±0.23*	–3.92±0.68*

Notes: *P<0.05 *vs*. 0 h in the same group; △P<0.05 *vs*. control group at the same time point

DISCUSSION

Ginsenosides and aconitine are the major components of SFI. Because of their excitatory action on alpha and beta receptors, ginsenosides and aconitine exert obviously protective effect on cardiovascular system. It has been shown that SFI can relieve blood vessel spasm and improve microcirculation, leading to decrease of peripheral vascular resistance and improvement of terminal microcirculation. Additionally, the other main function of SFI presents as enhancing cardiac function, elevating and stabilizing blood pressure, and protecting myocardial ischemia reperfusion injury. Therefore, SFI has been widely used in clinic in both prevention and treatment of some diseases, such as shock, all kinds of heart failure, arrhythmia, etc. At present, SFI was regarded as one of the commonly used drugs for the assistant treatment of shock in Chinese medicine.

As we all know, global end diastolic volume and cardiac output decreases, and blood pressure drops though heart rate increases in sepsis patients due to a variety of reasons, such as reduced systemic vascular resistance, abnormal distribution of microcirculation blood flow, and reduction of venous return. SFI could decrease myocardial injury, improve myocardial ultrastructure and reduce myocardial apoptosis.[8] SFI has two-way regulation on myocardium, and thus plays an important role in maintaining the stability of hemodynamics.[9] Many clinical trials confirmed that SFI could significantly increase the MAP and normalize HR.[10,11] In our study, we found that the hemodynamics of both groups of patients was improved after treatment. In the view of statistics, the levels of GEDI, MAP and CI were increased while the level of HR was decreased. However, the improvement in the control group was significantly less than that in the SFI group. These findings indicate that at least partially by enhancing myocardial contractility, SFI increases cardiac output and blood pressure, then improves tissue perfusion. Blood gas analysis show that microenvironment had been improved after treatment in both groups of patients with sepsis. The level of lactic acid in the SFI group decreased much more than that in the control group, suggesting that SFI may help improve the disorder of oxygen metabolism in sepsis patients.

In addition, there are many other studies proving that SFI can inhibit inflammatory factors, prevent excessive inflammatory reaction and suppress immune reaction.[12-15] But this is not the focus of the current study. Of note, ELWI showed no significant change among different time points in either SFI group or control group. There was also no remarkable difference between the two groups. It may be due to short monitoring time. Therefore, the effects of SFI on lung water and prognosis in patients with sepsis need to be further investigated based on evidence-based medicine.

Conflict of Interests

The authors have declared that no competing interests exist. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author Contributions

Fan KL, Kong L, Zhang FH and Hao H participated in the design of this study. Fan KL and Wang JH both performed the statistical analysis and drafted the manuscript. Zhao H, Tian ZY, Yin MX, Fang H, Yang HH and Liu Y provided assistance for data acquisition. All authors read and approved the final manuscript.

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