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Original Article

Effects of Ringer's sodium pyruvate solution on serum tumor necrosis factor-α and interleukin-6 upon septic shock

Wei Dong[1], Guannan Zhang[2], Feng Qu[3]

ABSTRACT

Objective: To study the effects of Ringer's sodium pyruvate solution on tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) upon septic shock.

Methods: Ninety emergency patients with septic shock were divided into treatment group and a control group by random draw. The control group was resuscitated with 50 ml of compound sodium chloride (Ringer's solution), and the treatment group was given 50 ml of Ringer's sodium pyruvate solution. Both groups were basically treated.

Results: All patients were successfully resuscitated. After treatment, extravascular lung water index, intrathoracic blood volume index, systemic vascular resistance index and cardiac index of the two groups were significantly improved compared with those before treatment ($P<0.05$). However, there were no significant inter-group differences at different time points ($P>0.05$). Blood lactic acid level, central venous oxygen saturation index and urine output were also improved after treatment, with significant inter-group differences ($P<0.05$). Serum TNF-α and IL-6 levels of both groups significantly decreased after treatment ($P<0.05$), and the levels of the treatment group were significantly lower than those of the control group ($P<0.05$). During 28 days of follow-up, the mortality rate of the treatment group (4.4%) was significantly lower than that of the control group (20.0%) ($P<0.05$).

Conclusion: Patients with septic shock are complicated with disordered expressions of inflammatory factors. During resuscitation, Ringer's sodium pyruvate solution can effectively promote blood circulation, mitigate inflammation and maintain acid-base equilibrium, thus decreasing the prognostic mortality rate.

KEY WORDS: Ringer's sodium pyruvate solution; Septic shock; Tumor necrosis factor-α; interleukin-6.

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INTRODUCTION

Septic shock, which refers to a medical condition induced by severe infection and sepsis, is mainly responsible for the deaths in intensive care unit (ICU) and thus troubling doctors worldwide.[1] When not treated timely, septic shock leads to cellular metabolism disorder, organ dysfunction, and even sudden death. Despite top-notch antibiotics, mechanical ventilation, monitoring and nutritional support, patients with septic shock are still prone to death.[2,3] Besides, rational intervention and diagnosis are in need to dynamically observe the pathological and biological processes.[4,5] Currently, septic shock

is mainly treated by controlling infection, as well as by supplementing circulating blood volume, recovering tissue perfusion and improving cellular metabolism with fluid resuscitation.[6,7]

Intravenous fluid resuscitation can rapidly recover blood volume, blood pressure, cardiac function and urine output, which is now mainly performed by using Ringer's solution to prevent adverse reactions.[8] Inflammatory factors play important roles in septic shock-induced organ dysfunction.[9] Once septic shock occurs, bacterial endotoxins and exotoxins as well as metabolites stimulate the release of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and oxygen radicals, resulting in toxic shock, organ dysfunction and death. As the key intermediate of glycolysis, pyruvic acid is the main constituent of energy metabolism and circulation and the center for metabolisms of carbohydrates, proteins and lipids in all tissues and organs of human body.[10]

Septic shock occurs based on uncontrollable inflammatory response induced by inflammatory mediators in early and advanced stages, during which considerable release of cytokines plays a crucial role. Cytokines have both pro- and anti-inflammatory effects which, if disturbed, will activate cascade reaction. Advanced-stage cytokines have long duration and interact with early-stage ones by positive feedback, being closely associated with the morality of septic shock.[11] TNF-α, as an initiator of inflammation, induces the secretion of other cytokines such as IL-1, IL-6, IL-8 and CSF and cooperates with them in inflammatory response.[12,13]

On the other hand, sodium pyruvate dialysate can facilitate the glycometabolism of shock cells, enhance systemic alkalization and antioxidant capacity, and protect organism from lactic acidosis.[14] Ringer's sodium pyruvate solution, which replaces sodium lactate with 28 mM sodium pyruvate, combines the advantages and have cytoprotective effects.[15] In this study, the effects of Ringer's sodium pyruvate solution on serum TNF-α and IL-6 upon septic shock were evaluated.

METHODS

Subjects: Ninety patients with septic shock enrolled in ICU of our hospital from February 2008 to November 2013 were selected in this study. This study has been approved by the ethic committee of our hospital, and written consent was obtained from all patients. Diagnostic criteria for septic shock: Severely infected patients who had uncorrected, persistent low blood pressure levels (systolic pressure < 90 mmHg, decrease by 40 mmHg compared with normal level, MAP < 60-40 mmHg, capillary refill time > 2, cold limbs or mottled skin, low urine output after sufficient fluid resuscitation, commonly accompanied by hypoperfusion or organ dysfunction.

Inclusion criteria: In accordance with the diagnostic criteria for septic shock; 20-80 years old; with written consent.

Exclusion criteria: ICU hospitalization stay length < 24 hour; use of drugs affecting immune function within six months; with autoimmune disease, acute cardiovascular disease, or HIV infection. The patients were divided into a treatment group and a control group by random draw (n=45), with similar gender, age, height, body weight and acute physiology and chronic health evaluation (APACHE) II score (P>0.05) (Table-I).

Resuscitation methods: All patients were treated according to their diseases and given sufficient anti-infective therapy and nutritional support. The control group was resuscitated by being intravenously injected with 50 ml of compound NaCl by using a microinjection pump for one hour (once every 12 h). By using the same method, the treatment group was resuscitated with 50 ml of Ringer's sodium pyruvate solution (50 mM sodium pyruvate). PiCCO plus monitor (Pulsion, Germany) was employed to adjust the injection dose and speed. The patients should be supplemented with fluids timely when extravascular lung water index (EVLWI) < 14 ml/kg and intrathoracic blood volume index (ITVBI) < 1000 ml/m^2. The fluid amount should be limited when EVLWI was lower than the normal level and ITVBI exceeded the

Table-I: Baseline clinical data.

Index	*Treatment group (n=45)*	*Control group (n=45)*	χ^2 *or t*	*P*
Gender (male/female)	25/20	24/21	0.067	>0.05
Age (years old)	56.33±4.12	56.29±5.01	0.045	>0.05
Body weight (kg)	60.39±10.38	60.57±9.32	0.293	>0.05
Height (cm)	165.39±11.67	165.02±12.00	0.193	>0.05
APACHE II score (point)	19.37±3.14	19.39±2.92	0.021	>0.05

Table-II: Hemodynamic indices before and after treatment (n=45, x±s).

	Index	*Before treatment*	*2 h after treatment*	*6 h after treatment*	*24 h after treatment*
Treatment group	ITVBI (ml/m²)	729.25±80.85	834.85±127.32*	945.12±137.42*	932.45±131.89*
	CI (L/min•m²)	3.1±1.2	3.5±1.3*	3.4±1.1*	3.4±1.1*
	SVRI (dyn.s.cm-5m²)	856.3±110.9	893.3±132.5	1018.2±151.4*	1722.3±114.5*
	EVLWI (ml/kg)	6.3±0.9	7.8±2.6*	9.3±3.1*	8.7±2.9*
Control group	ITVBI (ml/m²)	730.38±81.34	874.95±116.91*	942.91±113.04*	933.93±100.34*
	CI (L/min•m²)	3.1±1.3	3.4±1.0*	3.3±1.3*	3.3±1.0*
	SVRI (dyn.s.cm-5m²)	856.3±893	912.1±172.1	1010.3±100.8	1711.9±89.9*
	EVLWI (ml/kg)	6.3±0.9	7.7±2.5*	9.4±2.9	8.6±3.1

*Compared with the indices before treatment, P<0.05. ITVBI: intrathoracic blood volume ind[illegible], CI: c[illegible]iac index; SVRI: systemic vascular resistance index; EVLWI: extravascular lung water index.

Table-III: Central venous oxygen saturation, lactic acid level and urine output before and after treatment (n=45, x±s).

Group		*Central venous oxygen saturation*	*La[illegible]c ac[illegible] le[illegible] (mmol/*	*Urine output (ml/kg•h)*
Treatment group	Before resuscitation	45.7±2.3	7.4[illegible]	0.27±0.06Δ
	24 h after resuscitation	70.3±3.4*ΔΔ	3.1±1.6*Δ	0.51±0.10*ΔΔ
Control group	Before resuscitation	46.5±1.9	7.3±2.6	0.28±0.05Δ
	24 h after resuscitation	60.5±3.6*	[illegible]1.2*	0.37±0.13*

*Compared with the values before treatment,
P<0.05; Δcomparison between two groups after treatment, P<0[illegible]5.

normal level. When systolic pressure < 80 mmHg, additional vasoactive drugs were given. Whe[illegible] EVLWI was higher than the normal level, uri[illegible]-promoting therapy was given besides control[illegible]ng fluid amount.

Observation indices: Criteria for [illegible]ccessful resuscitation: Cardiac index (CI) >4.5 [illegible]min·m²), oxygen index >600 ml/(min·m²), [illegible]ygen consumption index > 170 ml/([illegible]m²). Monitoring of hemodynamic indices: IT[illegible]I, CI, systemic vascular resistance index (SVRI) and [illegible]WI were monitored before and two[illegible] 6 hour and 24 hour after treatment. Detectio[illegible] of c[illegible]ntral venous oxygen saturation, lactic acid [illegible]el a[illegible]d urine output: Central veno[illegible]xygen sa[illegible]on, lactic acid level and urine [illegible]put[illegible]ere detected before and 24 hour after tre[illegible]ent.

Detecti[illegible] of TNF-[illegible] and IL-6 levels: Fasting peripheral b[illegible]d (5 ml) was collected before and 24 h after treat[illegible]nt, left still and centrifuged at 2000 r/minutes for 20 minutes, from which the supernatant serum was collected and stored in a -80°C refrigerator prior to use. Afterwards, the levels of TNF-α and IL-6 were detected with double-antibody sandwich enzyme-linked immunosorbent assay according to the instructions of kit (Beijing Jingmei Biotech Co., Ltd., China). Investigation on prognostic survival: All patients were followed up for 28 days to observe their survival.

Sta[illegible] Analysis: All data were analyzed by SPSS 18.0. The means of categorical data were compared by t test and Wilcoxon rank-sum test. The numerical [illegible]ta were compared by Chi-square analysis. P<0.05 was considered statistically significant.

RESULTS

Hemodynamic indices: All patients were successfully resuscitated. ITVBI, SVRI and CI were improved two hour after treatment, with significant intra-group differences (P<0.05). EVLWI was also significantly improved six hour after treatment compared with that before treatment (P<0.05). However, there were no significant inter-group differences at different time points (P>0.05) (Table-II).

Central venous oxygen saturation, lactic acid level and urine output: Blood lactic acid level, central venous oxygen saturation index and urine output were also improved after treatment, with significant inter-group differences (P<0.05) (Table-III).

TNF-a and IL-6 levels: Serum TNF-α and IL-6 levels of both groups significantly decreased after treatment (P<0.05), and the levels of the treatment group were significantly lower than those of the control group (P<0.05) (Table-IV).

Mortality rate: During 28 days of follow-up, the mortality rate of the treatment group (4.4%) was significantly lower than that of the control group (20.0%) (P<0.05) (Table-V).

Table-IV: TNF-α and IL-6 levels before and after treatment (pg/ml, x±s).

Group	*Case number (n)*	*TNF-a*		*IL-6*	
		Before treatment	*After treatment*	*Before treatment*	*After treatment*
Treatment group	45	209.34±45.15	81.37±14.92	65.91±12.73	16.39±10.23
Control group	45	211.78±43.09	124.78±32.09	65.98±11.62	34.28±13.01
t		0.293	31.983	0.078	12.733
P		0.11	0.00	0.25	0.00

Table-V: Morality rates 28 days after treatment.

Group	*Case number (n)*	*Death*	*Morality rate*
Treatment group	45	2	4.4%
Control group	45	9	20.0%
χ^2			6.442
P			0.00

DISCUSSION

Septic shock results in hypovolemic shock, plummet of blood flow rate and flow, decreased oxygen-carrying capacity of red blood cells, organ tissue hypoperfusion, and dramatic metabolic changes, especially glucose metabolic disorder and acid-base disequilibrium, thereby inducing cellular metabolic disorder and organ dysfunction, and even multiple organ failure upon progression.[16] It is now well-established that septic sh[illegible] pathologically results from ischemia, anoxia [illegible]d reperfusion injury. Particularly, overproductio[illegible] of active oxygen and nitroxides triggers [illegible]ystemic inflammatory response syndrome t[illegible] renders septic shock from reversible to irreversi[illegible] being closely associated with progno[illegible]

In the early stage of septic sho[illegible]rforming anti-infection therapy in addition to flu[illegible]scitation can block or reduce the [illegible]roduction and release of inflammatory medi[illegible]ors, which is of great significance to the inhib[illegible]n of d[illegible]ease progression. Moreover, rati[illegible]nal interv[illegible] and diagnosis are required to [illegible]ically observe the pathological and biol[illegible]cal p[illegible]esses.[19] At present, septic shock is mainly [illegible]trolling infection, as well as by supp[illegible]enting circulating blood volume, recovering tiss[illegible]perfusion and benefiting cellular metabolism with fluid resuscitation.[20] An ideal fluid for resuscitation should be able to rapidly control infection, to shorten the shock time, and to prevent all kinds of complications. Nevertheless, requiring a large volume, fluid resuscitation easily induces organ circulation-perfusion, coagulopathy, etc. Recently, Ringer's solutions have been widely applied in experimental and clinical practice.[21]

Widely existing in human body, pyruvates are the intermediates of glycolysis and the metabolic centers of three essential nu[illegible]nts. Animal studies have verified that sodium pyr[illegible]e can treat shock and protect vital organs (e.g. br[illegible] and bowels) from injury, particularly in[illegible]iting [illegible] apoptosis of lung and brain cells and ma[illegible]g the intestinal mucosal barrier fu[illegible]tion. Exogenous supply of sodium pyruvat[illegible] ma[illegible]tains tricarboxylic acid cycle by augmen[illegible]ne[illegible]ctivity of pyruvic acid, so cons[illegible]derable e[illegible]s released to stabilize hemody[illegible]cs.[22] In this study, ITVBI, SVRI and CI were [illegible]ved two hour after treatment, with significant intra[illegible]up differences (P<0.05). EVLWI w[illegible]lso significantly improved six hour after t[illegible]tment compared with that before treatment (P<0.05). However, there were no significant inter-grou[illegible]ferences at different time points (P>0.05). Hence, abnormal distribution of systemic blood flow upon septic shock led to absolute or relative lack of effective circulating blood volume. In other words, resuscitation with Ringer's solution played a crucial role in treating septic shock and alleviating tissue perfusion. Treating patients with septic shock by Ringer's solution resuscitation as early as possible can significantly improve ITVBI and EVLWI as well as correct CI and SI. Regardless, EVLWI and CVP, especially those of severe patients, are bound to increase, but the temporary lung water increase hardly affects oxygenation and respiratory function.

Pathologically speaking, septic shock is a complicated process manifested as hypotension that leads to severe prognosis by inducing insufficient oxygen supply and energy metabolism disorders in organs, tissues and cells.[7] During metabolism and circulation, sodium pyruvate, through competitive inhibition, promotes the metabolism of the pentose phosphate pathway to generate NADPH and the recovery of glycometabolic oxidation. As a result, glycometabolic disorder is alleviated. Sodium pyruvate is superior to sodium lactate in correcting acidic environment at the early stage of severe shock because renal glycogen regeneration is subjected to compensatory enhancement Furthermore, sodium pyruvate prevents the generation of oxygen radicals by hindering the formation of peroxides,

and eliminates them by reacting with H_2O_2 to yield CO_2 and H_2O.[23] In this study, blood lactic acid level, central venous oxygen saturation index and urine output were also improved after treatment, with significant inter-group differences also (P<0.05), suggesting that Ringer's sodium pyruvate solution evidently relieved acidosis and benefited the reversal of refractory shock.

Resuscitation of septic shock is necessarily accompanied by tissue, organ ischemic reperfusion injuries during which acute liver, cardiac and gastrointestinal injuries are directly and/or indirectly induced, activating the inflammatory cascade also. In healthy human and locally inflammatory patients, inflammatory mediators released by activated inflammatory cells exert defensive effects at the sites of inflammation. These mediators damage vascular endothelial cells, dilate small blood vessels, raise the vascular wall permeability and contracts blood vessels and smooth muscles of other parts. Accordingly, patients may die of severe septic shock typified by hypotension and multiple organ dysfunction. IL-10, IL-4 receptor antagonists and other soluble anti-inflammatory molecules are the main an[ti]-inflammatory mediators, while TNF-α and IL-6 [are] potent proinflammatory factors. Terrible outcomes are inevitable once the inflammation b[alance] is destroyed. If the proinflammatory effe[ct] surpasses the anti-inflammatory effect, infl[ammatory] mediators intend to conti[nuously] pro[liferate] and to cause damages. In the [opposite] case, the possible compensatory anti-inflamm[atory] response syndrome results in immunoparalysis instead.[24] Serum TNF-α and IL-[6] levels of both groups herein significantly d[ecreased] after treatment (P<0.05), and the levels of the t[reatment] group were significantly [lower] than those of the control group (P<0.05), indicating that Ringer's sodium pyruvate solution [inhibits] inflammatory response after septic shock, mitigated oxygen free radical-induced proinflammatory response, and enhanced free radical-scavenging capacity.

TNF-α functions in septic shock by elevating body temperature as an endogenous pyrogen; by inducing vasodilation as well as decreases in blood pressure and tissue perfusion through producing copious NO; by destructing the integrity of vascular barrier both NO-dependently and NO-independently, which increases capillary permeability, enhances plasma extravasation and reduces venous return; by inhibiting the fibrinolytic system, which promotes the hemorrhagic necrosis of vital organs and even disseminated intravascular coagulation during septic shock. IL-6 is produced by monocytes and macrophages in the presence of IL-1 during inflammatory response, and it also facilitates the proliferation of T cells in cooperation with TNF-α. Upon severe infections and traumas, the produced catecholamine can significantly increase the plasma level of IL-6.[25]

It has previously been reported that after shock is resuscitated by intravenous injection, blood pressure and urine output are recovered, whereas systemic inflammatory response is gradually aggravated.[4] In this study, during 28 days of follow-up, the mortality rate of the treatment group (4.4%) was significantly lower than that of the control group (20.0%) (P<0.05), revealing that Ringer's sodium pyruvate solution managed to improve the prognosis, probably because resuscitation promoted systemic blood circulation, recovered intestinal barrier function and decreased inflammatory factors. In the meantime, this solution successfully facilitated intestinal microcirculation, corrected acidosis and protected the function of intestinal mucosal barrier.

In summary, patients with septic shock are complicated with disordered expressions of inflammatory factors. During resuscitation, Ringer's sodium pyruvate solution is capable of effectively promoting blood circulation, relieving inflammation and maintaining acid-base equilibrium, thereby lowering the prognostic mortality rate.

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Authors Contributions:

WD & FQ: Designed the protocol and prepared the final manuscript.
GNZ: Clinical data collection and experiments.