Journal of Hainan Medical University

http://www.hnykdxxb.com

Effect of continuous blood purification on inflammatory response, immune response and target organ damage in patients with sepsis

Cheng−Li Wang, Xue−Li Wang✉, Li Ma, Tian Fu, Gang Li

Department of Intensive Care Unit, Hanzhong 3201 Hospital in Shaanxi Province, Hanzhong City, Shaanxi Province, 723000

ARTICLE INFO

Article history:
Received 28 Jul 2017
Received in revised form 9 Aug 2017
Accepted 19 Aug 2017
Available online 28 Aug 2017

Keywords:
Sepsis
Continuous blood purification
Inflammatory response
Immune response
Target organ damage

ABSTRACT

Objective: To study the effect of continuous blood purification on inflammatory response, immune response and target organ damage in patients with sepsis. **Methods:** A total of 78 patients with sepsis who were treated in the hospital between January 2015 and December 2016 were collected and divided into control group and observation group according to the random number table method, 39 cases in each group. Control group received conventional therapy for sepsis, and observation group received continuous blood purification on the basis of conventional therapy. The differences in inflammatory response, immune response and target organ damage were compared between the two groups before and after treatment. **Results:** Before treatment, difference in serum inflammatory factor contents, peripheral blood Th17/Treg cellular immunity levels and serum myocardial injury marker contents were not statistically significant between the two groups. After treatment, serum IL-2, IL-6, PCT, CRP, NT-prBNP, CK, CK-MB, TnT and TnI contents as well as peripheral bloodTh17 and Treg cell levels and Th17/Treg proportion of both groups of patients were lower than those before treatment, and serum IL-2, IL-6, PCT, CRP, NT-prBNP, CK, CK-MB, TnT and TnI contents as well as peripheral blood Th17 and Treg cell levels and Th17/Treg proportion of observation group were lower than those of control group. **Conclusion:** Continuous blood purification can effectively reduce systemic inflammatory response, inhibit immune response, and reduce myocardial injury in patients with sepsis.

1. Introduction

Sepsis is the systemic inflammatory response syndrome (SIRS) caused by infection, it can quickly cause multiple tissue viscera function damage after it occurs, and severe cases can cause patients' death in the short term[1,2]. Anti-infection is the basic clinical therapy for sepsis, but many cases show that anti-infection therapy alone cannot effectively reverse the pathological process of sepsis, and it needs to be combined with other therapies to enlarge the curative effect. Continuous blood purification is the technology that continually eliminates toxin and macromolecular materials in circulation, and it has been successfully applied in the treatment of uremia, severe pancreatitis, poisoning and other critical diseases[3,4]. In the research, continuous blood purification technology was added to the clinical overall treatment of patients with sepsis, and its role was elaborated from inflammation, immune response and target organ damage, now reported as follows.

✉Corresponding author: Xue-Li Wang, Department of Intensive Care Unit, Hanzhong 3201 Hospital in Shaanxi Province, Hanzhong City, Shaanxi Province, 723000.
Tel: 13892620100
Fund Project: Social Development Key Project of Shaanxi Province No: 2012SF2-26.

2. Information and methods

2.1 General information

A total of 78 patients with sepsis who were treated in the hospital between January 2015 and December 2016 were selected, and the families of the patients signed informed consent. Inclusion criteria: (1) diagnosed with sepsis for the first time and never receiving treatment outside the hospital; (2) regularly receiving treatment and related examinations. Exclusion criteria: (1) combined with the serious infectious diseases of other tissue viscera; (2) combined with acute chronic hepatitis and nephritis; (3) combined with autoimmune diseases.

The enrolled patients were divided into the control group (n=39) and the observation group (n=39) according to the random number table method. Control group included 21 men and 18 women that were 37-72 years old; observation group included 22 men and 17 women that were 35-75 years old. The differences in the gender and age distribution were not significant between the two groups, the follow-up data were comparable, and the study was approved by the hospital ethics committee.

2.2 Therapy

Control group received routine clinical therapy for sepsis, which was specific as follows: parenteral nutrition support, broad spectrum antibiotic application, and anti-shock treatment.

Observation group, on the basis of conventional treatment, received continuous blood purification, specifically as follows: continuous high volume veno-venous hemofiltration mode was used, displacement liquid flow rate was 3 500 mL/min, the blood flow was 180-250 mL/min and single treatment lasted for 12-24 h. During the period, normal heparin anticoagulation was used to maintain APTT between 50-70 s.

2.3 Observation indexes

Before and after treatment, 5.0 mL of morning fasting peripheral blood was extracted from two groups of patients and anti-coagulated, 2.5 mL was directly frozen, and the other 2.5 mL was centrifuged at low speed to get upper serum, which was also stored in the cryogenic environment. The ELISA kit instructions were followed to determine the contents of serum inflammatory cytokines, including interleukin-2 (IL-2), interleukin-6 (IL-6), procalcitonin (PCT) and C-reactive protein (CRP). Flow cytometer (US BD Biosciences, model Flow Cytometer) was used to determine peripheral blood Th17/Treg cellular immunity level, including Th17 cells and Treg cells, and the proportion of Th17/Treg was calculated. Automatic electrochemical luminescence immunity analyzer (Roche Diagnostics GmbH, model Elecsys 2010) was used to determine the contents of myocardial injury markers, including N-terminal pro-brain natriuretic peptide (NT-prBNP), creatine kinase (CK), creatine kinase isoenzyme (CK-MB), troponin T (TnT) and troponin Ⅰ (TnI).

2.4 Statistical processing

Statistical software was SPSS 23.0. Inflammatory factors, Th17/Treg cellular immunity indexes, myocardial injury markers and other measurement data were in terms of mean ± standard deviation, and comparison was by t test. $P<0.05$ indicated statistical significance in differences.

3. Results

3.1 Inflammatory factors

Before and after treatment, comparison of serum inflammatory factors IL-2 (pg/mL), IL-6 (pg/mL), PCT (ng/mL) and CRP (g/L) contents between two groups of patients was as follows: before treatment, serum IL-2, IL-6, PCT and CRP contents were not statistically different between the two groups ($P>0.05$). After treatment, serum IL-2, IL-6, PCT and CRP contents of both groups of patients were lower than those before treatment ($P<0.05$), and serum IL-2, IL-6, PCT and CRP contents of observation group were lower than those of control group ($P<0.05$), shown in Table 1.

Table 1.
Comparison of serum IL-2, IL-6, PCT and CRP contents before and after treatment.

Groups	n	Time	IL-2	IL-6	PCT	CRP
Control group	39	Before treatment	172.39±21.75	114.28±14.26	10.27±1.84	35.38±4.29
		After treatment	115.62±13.46*	79.61±8.54*	7.15±0.84*	24.71±3.06*
Observation group	39	Before treatment	171.84±20.59	113.79±13.85	10.35±1.79	35.27±4.18
		After treatment	58.19±7.25*#	47.23±5.61*#	2.09±0.26*#	9.63±0.98*#

Note: comparison of indexes between before and after treatment within group, *$P<0.05$; comparison of indexes between observation group and control group after treatment, #$P<0.05$.

Table 2.
Comparison of Th17/Treg cellular immune state before and after treatment.

Groups	n	Time	Th17	Treg	Th17/Treg
Control group	39	Before treatment	5.48±0.69	12.73±1.95	2.84±0.35
		After treatment	4.17±0.48*	9.62±0.98*	2.45±0.31*
Observation group	39	Before treatment	5.45±0.63	12.68±1.89	2.81±0.32
		After treatment	3.09±0.38*#	6.15±0.74*#	2.09±0.24*#

Note: comparison of indexes between before and after treatment within group, *$P<0.05$; comparison of indexes between observation group and control group after treatment, #$P<0.05$.

Table 3.
Comparison of serum NT-prBNP, CK, CK-MB, TnT and TnI contents before and after treatment.

Groups	*n*	Time	NT-prBNP	CK	CK-MB	TnT	TnI
Control group	39	Before treatment	1 037.61±158.36	26.48±3.17	30.49±3.74	593.26±64.28	452.28±56.19
		After treatment	713.24±89.64*	21.53±2.79*	21.35±2.79*	319.83±35.72*	307.16±35.74*
Observation group	39	Before treatment	1 035.98±173.25	26.39±3.42	30.62±3.84	594.52±61.53	456.73±54.27
		After treatment	342.86±45.71*#	13.25±1.84*#	12.35±1.76*#	165.28±21.63*#	150.25±18.93*#

Note: comparison of indexes between before and after treatment within group, $^{*}P<0.05$; comparison of indexes between observation group and control group after treatment, $^{\#}P<0.05$.

3.2 Th17/Treg cellular immunity

Before and after treatment, comparison of peripheral blood Th17/Treg cellular immunity index levels between two groups of patients was as follows: before treatment, peripheral blood Th17/Treg cell levels and Th17/Treg proportion were not statistically different between the two groups ($P>0.05$). After treatment, peripheral blood Th17 and Treg cell levels as well as Th17/Treg proportion of both groups of patients were lower than those before treatment ($P<0.05$), and peripheral blood Th17 and Treg cell levels as well as Th17/Treg proportion of observation group were lower than those of control group ($P<0.05$), shown in Table 2.

3.3 Myocardial injury markers

Before and after treatment, comparison of serum myocardial injury markers NT-prBNP (pg/mL), CK (U/L), CK-MB (U/L), TnT (μg/L) and TnI (μg/L) contents between two groups of patients was as follows: before treatment, serum NT-prBNP, CK, CK-MB, TnT and TnI contents were not statistically different between the two groups ($P>0.05$). After treatment, serum NT-prBNP, CK, CK-MB, TnT and TnI contents of both groups of patients were lower than those before treatment ($P<0.05$), and serum NT-prBNP, CK, CK-MB, TnT and TnI contents of observation group were lower than those of control group ($P<0.05$), shown in Table 3.

4. Discussion

Sepsis has been the emphasis and difficulty of clinical treatment, routine anti-infection and anti-shock treatment can alleviate the illness severity to a certain extent, but they are limited in containing the disease progress, and some patients still have important organ dysfunction, and even develop multiple organ dysfunction syndrome (MODS), resulting in death in patients[5-7]. Continuous blood purification is a reliable technology for treatment of serious infectious diseases at present, which eliminates toxins and macromolecular materials in the circulation to maintain homeostasis and sound important tissue viscera function, and thus improve the survival rate of patients[8,9]. The core mechanism of sepsis is that toxin infection causes severe SIRS, so the application of continuous blood purification is expected to improve the illness severity, but the current related research results mainly stay in the overall application effectiveness of the technique, and less focus on the impact on hematology indexes. In the research, continuous blood purification was used for the adjuvant treatment of patients with sepsis, and its effect on the inflammatory response, immune response, target organ damage and other aspects was mainly explored to lay a foundation for subsequent selection of clinical disease therapy.

The secretion of a large number of inflammatory factors and the emergence of SIRS are the basic pathological mechanisms of sepsis, so the degree of inflammatory reaction can objectively reflect the severity of sepsis[10,11]. IL-2 and IL-6 are typical pro-inflammatory factors, which are induced by CRP, further attract neutrophils to gather and release more inflammatory mediators so as to form a cascade of inflammation[12,13]. PCT is a new inflammatory marker, also known as the advanced inflammatory factor, and its content gradually increases 48 h after the inflammatory response, and is highly consistent with the severity of infection[14]. In this study, the differences in contents of above inflammatory factors were compared between the two groups, and it was found that compared with those before treatment, serum IL-2, IL-6, PCT and CRP contents of both groups of patients decreased after treatment; further compared with those of control group, serum IL-2, IL-6, PCT and CRP contents of observation group were lower, showing that continuous blood purification technology application in the overall treatment can effectively restrain the systemic inflammatory response, which is the direct performance of the remission of sepsis.

Patients with sepsis can show various immune function abnormalities, and Th17/Treg cellular immune response abnormality is one of the more important ones[15,16]. Th17 cells express ROR γ t, secrete IL-17, can exert positive pro-inflammatory effect and participate in the formation of SIRS. Treg cells and Th17 cells inhibit each other and are negatively regulated in function, and the broken balance of the two can lead to immune disorders[17]. In this study, differences in Th17/Treg cellular immune status were compared between the two groups, and it was found that compared with those before treatment, Th17 and Treg cell levels as well as the Th17/Treg proportion in peripheral blood of both groups were lower, indicating that both therapies can prompt Th17/Treg cellular immunity tend to balance; further compared with control group, the observation group were with lower Th17 and Treg cell levels as well as the proportion of Th17/Treg in peripheral blood, confirming that after continuous blood purification technology application in overall treatment, Th17 cell and Treg cell function are inhibited to different degree, and the

Th17/Treg cellular immunity progresses to the advantage of Treg cells.

Patients with sepsis can have multiple organ damage, which is one of the most important causes of death. Myocardium is the mostly easily involved viscera, both toxins and inflammatory factors can lead to myocardial cell membrane injury and dysfunction, and many kinds of factors inside the cells are secreted into the outside during this time and detected in serum, which are clinically called myocardial injury markers. NT-prBNP has become an important biochemical marker for the diagnosis of heart disease, and the NT-prBNP massively secreted in the serum of sepsis patients is a sign of the decline of myocardial function[18]. CK, CK-MB, TnT and TnI all belong to the myocardial enzyme spectrum indexes, which are highly expressed in patients with myocardial infarction and heart failure, and can quantitatively reflect the degree of myocardial injury[19,20]. In this study, the differences in serum levels of above myocardial injury markers were compared between the two groups, and it was found that compared with those before treatment, serum NT-prBNP, CK, CK-MB, TnT and TnI contents of both group decreased after treatment, indicating that both treatments can achieve a certain degree of myocardial protection; further compared with control group, the observation group were with lower serum NT-prBNP, CK, CK-MB, TnT and TnI contents after treatment, confirming that the continuous blood purification can effectively reduce the myocardial injury in patients with sepsis and achieve a more positive myocardial protection effect.

Continuous blood purification technique can help to reduce the systemic inflammatory response and equalize immune response in patients with sepsis, and also play a positive role in myocardial protection. It is recommended to add continuous blood purification techniques in the future clinical treatment of patients with sepsis,.

References

[1] Kortz TB, Axelrod DM, Chisti MJ, Kache S. Clinical outcomes and mortality before and after implementation of a pediatric sepsis protocol in a limited resource setting: A retrospective cohort study in Bangladesh. *PLoS One* 2017; **12**(7): e0181160.

[2] Panpetch W, Somboonna N, Bulan DE, Issara-Amphorn J, Finkelman M, Worasilchai N, et al. Oral administration of live- or heat-killed Candida albicans worsened cecal ligation and puncturesepsis in a murine model possibly due to an increased serum (1→3)- β -D-glucan. *PLoS One* 2017; **12**(7): e0181439.

[3] Putzu A, Fang MX, BoscoloBerto M, Belletti A, Cabrini L, Cassina T, et al. Blood purification with continuous veno-venous hemofiltration in patients with sepsis or ARDS: a systematic review and meta-analysis. *Minerva Anestesiol* 2017; **83**(8): 867-877.

[4] Kraj inovi SS, Doronjski A, Barisi N, Stojanovi V. Risk factors for neonatal sepsis and method for reduction of blood culture contamination. *Malawi Med J* 2015; **27**(1): 20-24.

[5] Andaluz D, Ferrer R. SIRS, qSOFA, and organ failure for assessing sepsis at the emergency department. *J Thorac Dis* 2017; **9**(6): 1459-1462.

[6] Molnar L, Nemeth N, Berhes M, Hajdu E, Papp L, Molnar A, et al. Assessment of cerebral circulation in a porcine model of intravenously given E. coli induced fulminantsepsis. *BMC Anesthesiol* 2017; **17**(1): 98.

[7] Rochwerg B, Millen T, Austin P, Zeller M, D'Aragon F, Jaeschke R, et al. Fluids in Sepsis and Septic Shock (FISSH): protocol for a pilot randomised controlled trial. *BMJ Open* 2017; **7**(7): e017602.

[8] Jiang Y, Lin R, Xu Y, Zhang S, Cui K, Zhu M, et al. Continuous blood purification treatment for endotoxin-induced acute respiratory distress syndrome. *Braz J Med Biol Res* 2017; **50**(2): e5367.

[9] Dai SR, Li Z, Zhang JB. Serum interleukin 17 as an early prognostic biomarker of severe acute pancreatitis receivingcontinuous blood purification. *Int J Artif Organs* 2015; **38**(4): 192-198.

[10]Virzi GM, Clementi A, Brocca A, de Cal M, Marcante S, Ronco C. Cardiorenal syndrome type 5 in sepsis: role of endotoxin in cell death pathways and inflammation. *Kidney Blood Press Res* 2016; **41**(6): 1008-1015.

[11]Mertens K, Lowes DA, Webster NR, Talib J, Hall L, Davies MJ, et al. Low zinc and selenium concentrations in sepsis are associated with oxidative damage and inflammation. *Br J Anaesth* 2015; **114**(6): 990-999.

[12]Pfeiffer D, Roßmanith E, Lang I, Falkenhagen D. miR-146a, miR-146b, and miR-155 increase expression of IL-6 and IL-8 and support HSP10 in an In vitro sepsis model. *PLoS One* 2017; **12**(6): e0179850.

[13]Negrin LL, Jahn A, van Griensven M. Leptin protects against mortality and organ dysfunction in a two-hit trauma/sepsis model and isil-6-dependent. *Shock* 2017; **48**(1): 130-137.

[14]Cabral L, Afreixo V, Almeida L, Paiva JA. The use of procalcitonin (pct) for diagnosis of sepsis in burn patients: a meta-analysis. *PLoS One* 2016; **11**(12): e0168475.

[15]Jeremias IC, Victorino VJ, Barbeiro HV, Kubo SA, Prado CM, Lima TM, et al. The role of acetylcholine in the inflammatory response in animals surviving sepsis induced by cecal ligation and puncture. *Mol Neurobiol* 2016; **53**(10): 6635-6643.

[16]Jeremias IC, Victorino VJ, Machado JL, Barroso WA, Ariga SK, Lima TM, et al. The severity of cecal ligature and puncture-induced sepsis correlates with the degree of encephalopathy, but the sepsis does not lead to acute activation of spleen lymphocytes in mice. *Mol Neurobiol* 2016; **53**(5): 3389-3399.

[17]Li J, Li M, Su L, Wang H, Xiao K, Deng J, et al. Alterations of T helper lymphocyte subpopulations in sepsis, severe sepsis, and septic shock: a prospective observational study. *Inflammation* 2015; **38**(3): 995-1002.

[18]Tettamanti C, Hervet T, Grabherr S, Palmiere C. Elevation of NT-proBNP and cardiac troponins in sepsis-related deaths: a forensic perspective. *Int J Legal Med* 2016; **130**(4): 1035-1043.

[19]Zhang L, Yao J, Wang X, Li H, Liu T, Zhao W. Poly (ADP-ribose) synthetase inhibitor has a heart protective effect in a rat model of experimentalsepsis. *Int J Clin Exp Pathol* 2015; **8**(9): 9824-9835.

[20]Zhou L, Gao M, Xiao Z, Zhang J, Li X, Wang A. Protective effect of astaxanthin against multiple organ injury in a rat model of sepsis. *J Surg Res* 2015; **195**(2): 559-567.