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Efficacy of continuous renal replacement therapy in the treatment of severe acute pancreatitis associated acute respiratory distress syndrome

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Abstract. – OBJECTIVE: To investigate the efficacy of the treatment of severe acute pancreatitis (SAP) complicated by acute respiratory distress syndrome (ARDS) using continuous renal replacement therapy (CRRT) by evaluating the effect of CRRT on respiratory and circulatory function as well as serum cytokines level.

PATIENTS AND METHODS: Fifty four randomly selected patients with confirmed SAP complicated by ARDS after being admitted to intensive care unit (ICU) within 72 hr of onset were included in the study. Patients received mechanical respiratory support and CRRT. Arterial blood gas analysis was conducted and serum cytokine levels, including tumor necrosis factor alpha (TNF-α), interleukin 4 (IL-4) and interleukin 6 (IL-6), as well as C reactive protein (CRP) were evaluated respectively both before and 6h, 12h, and 24h after CRRT therapy. Peak inspiratory pressure and pulmonary compliance were also recorded.

RESULTS: Arterial oxygen tension (PaO_2), oxygenation index (OI) as well as dynamic pulmonary compliance were all elevated significantly, whereas peak inspiratory pressure significantly decreased at 6h, 12h and 24h after CRRT respectively; serum cytokine level and CRP significantly decreased ($p < 0.05$).

CONCLUSIONS: CRRT can effectively reduce the level of inflammatory mediators, and improve respiratory and circulatory function.

Key Words:
Continuous renal replacement therapy, Severe acute pancreatitis, Acute respiratory distress syndrome.

Introduction

Severe acute pancreatitis (SAP) is a common type of serious surgical condition, frequently accompanied by multiple organ failure and severe local complications with higher mortality. With the deepening understanding of underlying mechanism and pathophysiology of SAP, significant progress has been achieved in the management of SAP, for example, by using renal replacement therapy[1]. Early intervention using renal replacement therapy can reduce the peaking of inflammatory mediators, diminish the extent of systemic inflammatory reactions, improve respiratory function in patients with SAP associated acute respiratory distress syndrome (ARDS), decrease APACHE (Acute Physiology and Chronic Health Evaluation) II score and improve the restoration of respiratory and circulatory functions.

In this article, we report our case load in the treatment of 54 patients with SAP complicated with ARDS using continuous renal replacement therapy.

Patients and Methods

Patients

Between January 2002 and December 2009, 54 patients with SAP accompanied with ARDS who were admitted to ICU of our institution within 72h of onset of the disease were randomly selected for inclusion in our study. Thirty six men average age of (50.6 ± 14.9) years and 18 women with average age of (50.6 ± 17.8) years were enrolled. The average age of all patients was (50.6 ± 15.6) years. All patients' conditions were confirmed in accordance with the criteria of the Atlanta definition of SAP and underwent mechanical respiratory support. No contraindications for renal replacement therapy were observed.

Treatment

Routine Treatment

Patients received routine therapy for SAP[3] in addition to mechanical ventilation in either posi-

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tive-end expiratory pressure (PEEP) or bi-phasic airway pressure ventilation (BIPAP) mode. The routine management of SAP included gastrointestinal decompression, fasting, parenteral nutritional support, fluid restoration therapy, administration of antibiotics, somatostatin as well as rhubarb.

Renal Replacement Therapy

Continuous veno-venous hemofiltration (CVVH) with predilution replacement solution at various flow rates, ranging from 2000 to 2500 ml/h, and blood flow ranging from 100 to 150 ml/h was adopted in all patients using a PRISMA automatic hemofiltration system (Gambro, Lund, Sweden) with polysulfone filters (AV600S Dialyzer; Fresenius Medical Care, Bad Homburg, Germany). The replacement solution was composed of 2000 ml normal saline, 5% glucose solution 500 ml, 25% magnesium sulfate solution 1ml, 10% calcium gluconate 10 ml and 5% sodium bicarbonate 125 ml. For patients without detectable hyperkalemia, 10% potassium chloride 7.5 ml was added to replacement solution (4). The formula of replacement solution was adjusted according to blood glucose level and electrolytes level of patients. Insulin was administrated when necessary. Conventional heparin was used as anticoagulant. CRRT was performed without using heparin in 5 patients with severe bleeding tendency.

Parameters Monitored

APACHE (Acute Physiology and Chronic Health Evaluation) II score was assessed both before and after the treatment. Patients' blood samples were collected before CRRT treatment and at 6h, 12h, and 24h after the treatment. Arterial blood gas analysis was performed at the aforementioned time points, and concentrations of serum cytokines including tumor necrosis factor alpha (TNF-α), interleukin 4 (IL-4) and interleukin 6 (IL-6) as well as C reactive protein (CRP) were evaluated. Furthermore, peak inspiratory pressure and pulmonary compliance were also recorded.

Statistical Analysis

All data is presented as mean ± standard deviation. Statistical analysis was performed using SPSS 11.5 software (SPSS Inc., Chicago, IL, USA). ANOVA tests were performed, pairwise comparisons of means were conducted using q test and difference between two independent samples was conducted using *t* test. A p value < 0.05 was considered statistically significant.

Results

APACHE II Score

The average APACHE II score after CRRT (18.5 ± 3.4) was significantly lower than that before treatment (23.5 ± 5.4) ($p < 0.01$).

Respiratory Function

Arterial oxygen tension (PaO_2), oxygenation index (OI) as well as dynamic pulmonary compliance were all elevated significantly, whereas peak inspiratory pressure significantly decreased at 6h, 12h and 24h after CRRT respectively ($p < 0.05$) (Table I).

Cytokines and CRP Levels

Compared with the levels before CRRT treatment, serum cytokines including TNF-α, IL-4 and IL-6 as well as CRP significantly decreased ($p < 0.05$) at 6h after CRRT (Table II).

Discussion

ARDS is one of severe complications associated with SAP. SAP will induce massive inflam-

Table I. Comparison of respiratory function before and after CRRT.

Time point	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	PaO_2/FiO_2	pH	Ppeak (cm H_2O)	(l/cm H_2O)
Before CRRT	56 ± 14	34 ± 12	102 ± 24	7.24 ± 0.12	35.5 ± 6.3	17.6 ± 4.6
6h after CRRT	65 ± 17*	40 ± 9*	155 ± 34*	7.35 ± 0.13*	26.2 ± 3.9*	23.3 ± 4.2*
12h after CRRT	74 ± 12*	39 ± 8*	162 ± 27*	7.36 ± 0.16*	25.3 ± 2.3*	22.3 ± 5.4*
24h after CRRT	75 ± 11*	40 ± 6*	195 ± 20*	7.35 ± 0.21*	26.9 ± 0.1*	24.1 ± 6.5*

*VS. assessment before CRRT, $p < 0.05$. 1 mmHg = 0.133 kPa. 1 cm H_2O = 0.098 kPa.

Table II. Changes in serum cytokine concentrations after CRRT.

Time point	TNF-α (mg/ml)	IL-6 (pg/ml)	IL-4 (ng/ml)	CRP (mg/L)
Before CRRT	5.32 ± 0.74	124 ± 31	0.55 ± 0.14	42.3 ± 5.1
6h after CRRT	3.18 ± 0.44 *	97 ± 21*	0.46 ± 0.16*	25.2 ± 3.6*

*VS. before CRRT $p < 0.05$.

matory response, activate effector cells which release large amount of cytokines and inflammatory mediators, resulting in severe inflammatory response syndrome (SIRS). Lungs contain a reservoir of effector cells which will be attracted by, migrated to and aggregated at the lesion in response to inflammatory signals. In the progression of SIRS, effector cells will be activated by inflammatory mediators, leading to respiratory failure. Considering this, lung is the earliest affected target of ARDS[6]. Activation of inflammatory cells can trigger the excessive and lasting release of inflammatory mediators, leading to a cascade of chain reactions. Therefore, timely clearance of circulatory inflammatory mediators and blocking the progression of inflammatory reactions are the key to improving the success rate of treatment in ARDS.

APACHE II score is a predictor of organ failure and mortality by evaluating patients' physiological conditions on admission and previous health status, as well as physiological changes during treatment. These provide evidence for improving quality of treatment and rationalizing the distribution of medical resources[7]. The APACHE II score system also plays an important role in the treatment and prognostic evaluation of SAP[8,9]. In this study, APACHE II score at 24h after CRRT (18.5 ± 3.4) was significantly decreased from that before treatment (23.5 ± 5.4) ($p < 0.01$). PaO_2, OI as well as dynamic pulmonary compliance were all elevated significantly, whereas peak inspiratory pressure significantly decreased at 6h after CRRT. Vital signs of patients were stabilized and dyspnea and hypoxemia were significantly relieved.

Currently, hemofiltration is the only effective method for the clearance of excessive cytokines. It can terminate cascade inflammatory reactions by reducing peak concentration of cytokines, thus, delaying the occurrence of multiple organ dysfunction[10]. The clearance of circulatory inflammatory mediators by hemofiltration is related to the phase of cytokine release[11]. Excessive production of inflammatory mediators in SAP induces the occurrence of SIRS, causing damage to multiple organs, including the pancreas[12]. In cases when systemic inflammatory reactions occurs at the early stage of disease, CRRT can eliminate circulatory inflammatory mediators, block the progression of systemic inflammatory reaction, inhibit the release of pro-inflammatory factors (TNF-α, IL-4, etc.) and prevent pancreatic necrosis[13], thereby, improving the success rate of rescuing SAP associated ARDS. In this study, serum cytokines including TNF-α, IL-4 and IL-6 as well as CRP significantly decreased after CRRT. Considering all the evidence, for patients not presenting with any indications for surgery, intervention using continuous venous-venous hemofiltration (CVVH) within 72 h of onset of the disease can effectively promote the dynamic balance between pro- and anti-inflammatory cytokines and reduce peak value of cytokines, relieving diffuse inflammatory reactions in the lungs and promoting the healing of inflammation.

Systemic inflammatory response causes influx of inflammatory cells and fluid to the pulmonary interstitium in patients with SAP associated ARDS[14]. Minimizing fluid intake while ensuring adequate tissue perfusion is an important strategy at the early stage of the disease.

Conclusions

This study suggested that CRRT can effectively reduce the level of inflammatory mediators, decrease APACHE II score, improve respiratory function and promote the restoration of respiratory and circulatory functions in patients with SAP associated ARDS.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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