European Review for Medical and Pharmacological Sciences 2016; 20: 873-878

Early blood purification therapy of severe acute pancreatitis complicated by acute lung injury

H. GUO[1], D.-W. SUO[1], H.-P. ZHU[2], X.-M. SUN[3], J. CHEN[1]

[1]Department of Emergency, The Fifth Affiliated Hospital of Zhengzhou University, Zhengzhou, China
[2]Department of Urology, The Fifth Affiliated Hospital of Zhengzhou University, Zhengzhou, China
[3]Department of Gastroenterology, The Tenth People's Hospital Affiliated to Tongji University, Shanghai, China

Abstract. – OBJECTIVE: Severe acute pancreatitis (SAP) can often be complicated by acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), leading to increased mortality. Early blood purification clears inflammatory cytokines and promotes immune function recovery. Here we evaluated the usefulness of this therapy in SAP complicated by ALI.

PATIENTS AND METHODS: 32 patients received routine treatment (control group), whereas other 32 patients received routine treatment and early blood purification therapy (study group). We evaluated respiratory indexes (PaO_2, PaO_2/FiO_2, alveolar-arterial oxygen difference, intrapulmonary arteriovenous shunt percentage, and respiratory rate), blood biochemical (creatinine, blood urea nitrogen, alanine aminotransferase, and lactate levels) and inflammatory (CRP, IL-10, TNF-α, and IL-10/TNF-α ratio) markers, and prognostic outcomes (multiple organ dysfunction syndrome [MODS] and APACHE II scores) before and 72 hours after the treatment. We also documented mechanical ventilation use, occurrence of MODS and ARDS, and mortality rates.

RESULTS: There were no deaths. Mechanical ventilation was used in a similar percentage of patients in either group. Treatment in study group led to a faster and better recovery of respiratory indexes, and less pronounced changes in the levels of blood urea nitrogen and alanine aminotransferase. Inflammatory markers also normalized better in the study group. Furthermore, MODS and APACHE II scores decreased to a greater extent in the study group, paralleled by a lower occurrence of MPDS and ARDS.

CONCLUSIONS: Early blood purification therapy improves respiratory function and inflammatory markers in patients with SAP complicated by ALI, and decreases the occurrence of MODS and ARDS.

Key Words:
Blood purification, Severe acute pancreatitis, Acute lung injury, Treatment, Efficacy.

Introduction

Severe acute pancreatitis (SAP) is an acute clinical gastrointestinal disorder caused by a release of high levels of inflammatory mediators in the pancreas. SAP can evolve as a localized disease as well as part of the multiple organ dysfunction syndrome (MODS). The latter leads to high mortality[1]. SAP is often associated with pathological changes in the lungs. Thus, SAP can be complicated by acute lung injury (ALI) in as often as 60% to 70% of cases. Further more, ALI can often be followed by acute respiratory distress syndrome (ARDS), and the latter is the main cause of death in patients with SAP[2]. Therefore, early prevention and treatment of ALI are crucial to improving the quality of life and prognosis of patients with SAP.

Early blood purification is capable of clearing inflammatory cytokines produced at inflamed sites. This therapy promotes the recovery of immune function and stabilizes the internal environment. Therefore, it is widely used in the treatment of inflammatory response syndrome, MODS, and other diseases[3]. In the present report, we evaluated the usefulness of early blood purification in the treatment of SAP complicated by ALI.

Patients and Methods

Patients

This study was approved by the Medical Ethics Committee of Experts of our Hospital, and

Corresponding Author: Hua Guo, MD; e-mail: guohua47629@163.com

informed consents of patients and their families were gathered. In total, we enrolled 64 patients with SAP complicated by ALI who were treated in our Hospital from May 2008 to May 2015. These patients were randomly divided into study and control groups, each comprising 32 patients. The demographic and clinical characteristics of study patients are presented in Table I. Both groups were comparable for all studied characteristics.

Inclusion and Exclusion Criteria

Inclusion criteria were the following: (1) diagnosis of SAP according to the diagnostic criteria developed by the Chinese Medical Association[4], (2) diagnosis of ALI according to the diagnostic criteria developed by Chinese Medical Society of Respiratory Diseases[5], (3) time from the onset of admission of ≤ 72 hours, and (4) age ranging between 18 and 70 years old. Exclusion criteria comprised (1) treatment time of ≤ 24 hours, (2) administration of mechanical ventilation at admission, (3) pre-existing chronic lung disease or a history of left ventricular dysfunction, and (4) MODS or kidney failure or other severe condition.

Treatments

All patients received routine treatment for SAP complicated by ALI[6] which included fasting, gastrointestinal decompression, fluid infusion, analgesia, oxygen inhalation, and respiratory physical therapy. Patients' water-electrolyte imbalance and metabolic acid-base imbalance were actively corrected. In parallel, drugs suppressing pancreatic secretion and inhibiting gastric acid secretion, and antibiotics were administered.

In addition to the above therapeutic measures, early blood purification was administered in patients of the study group. Specifically, they were treated with early continuous blood purification therapy within 24 hours after admission[7]. The Seldinger vascular access technique was used to establish the internal jugular or femoral vein paths by indwelling double lumen catheter, and blood flow were adjusted to 200-250 mL/min. Replacement fluid was purchased from the General Hospital of Nanjing Military Region and administered at a flow rate of 4 L/hour. The utilized equipment included BM25 continuous renal replacement hemodialysis machine (Baxter Company, Deerfield, IL, USA), EQUAsmart continuous hemofiltration machine (Medica S.r.l., Parma, Italy), and B. Braun Avitum AG polysulfone membrane dialyzers (Braun, Pfieffewiesen, Melsungen, Germany). Utilized filters were Filtral 16 (AN69 HF, Hospal Industrie, Meyzieu, France) with an area of 116 m^2. If clotting occurred, the filter was immediately replaced. A saline flush filter was utilized every 2 hours if no clotting occurred. The filter was replaced once every 24 hours. During blood purification, low molecular weight heparin (first dose of 3000-5000 U, and an additional dose of 200-600 U/hour) combined with sodium citrate was used for anticoagulation. If patients exhibited a tendency to severe bleeding, only sodium citrate was used. If patients exhibited severe acidosis or lacked calcium ions, only low molecular weight heparin was used. Early blood purification continued for 3 days. If patients had renal dysfunction during treatment, the replacement fluid flow rate was decreased to 2 L/hour[8].

Outcome Measures

Arterial blood was extracted before treatment, and 24, 48, and 72 hours after the treatment. The i-STAT 300 blood gas analyzer (Abbott, Abbott Park, IL, USA) was used to detect arterial oxygen tension (PaO_2), oxygenation index (PaO_2/FiO_2), alveolar-arterial oxygen difference [(A-a) DO_2], intrapulmonary arteriovenous shunt percentage (Qs/Qt), and respiratory rate (R) to observe changes in respiratory function.

Furthermore, we assessed biochemical parameters in venous blood. Fasting venous blood was drawn before and 72 hours after the treatment. The BS-200 automatic biochemical analyzer (Mindray, Shenzhen, China) was used to detect creatinine (Cr), blood urea nitrogen (BUN), alanine aminotransferase (ALT), and lactate levels.

Further outcomes were systemic levels of inflammatory cytokines and prognostic outcomes. For evaluation of inflammatory cytokines, fasting venous blood was drawn before and 72 hours after the treatment. ELISAs were used to detect serum C-reactive protein (CRP), interleukin-10 (IL-10), and tumor necrosis factor-α (TNF-α) levels. The IL-10/TNF-α ratio[9] was also calculated. Prognostic outcomes included MODS and APACHE II scores before and 72 hours after the treatment. Furthermore, we documented the use of mechanical ventilation, MODS and ARDS occurrence rates, and mortality rates.

Statistical Analysis

Data were analyzed using SPSS18.0. Categorical data were presented as absolute numbers (%), and compared using the chi-square test. Continuous data were presented as mean ± SEM and compared using the *t*-test. The test level was set to $\alpha = 0.05$, and the *p*-value of < 0.05 was considered as indicating statistically significant differences.

Table I. Patient demographic and clinical characteristics

Characteristics		Study group (n = 32)	Control group (n = 32)	*p*
Age (years)		52.31 ± 11.96	51.58 ± 12.64	n.s.
APACHE II score (points)		20.37 ± 4.58	20.61 ± 3.58	n.s.
Onset time of ALI after development of SAP (days)		4.47 ± 3.51	4.60 ± 3.28	n.s.
Gender	Male	21 (65.6)	23 (71.9)	n.s.
	Female	11 (34.4)	9 (28.1)	
Smoking history	Yes	17 (53.1)	18 (56.3)	n.s.
	No	15 (46.9)	14 (43.8)	
History of chronic disease	Yes	26 (81.3)	25 (78.1)	n.s.
	No	6 (18.8)	7 (21.9)	

Footnote: Data are mean ± SEM or absolute numbers (%). n.s.: not significant.

Results

Respiratory Function Outcomes

We observed that in the study group, PaO_2 and PaO_2/FiO_2 significantly increased, whereas (A-a) DO_2, Qs/Qt, and R significantly decreased, 24 hours after the treatment (Table II). These changes occurred earlier than in control group which exhibited significant changes only 48 hours after the treatment (Table II). Seventy-two hours after the treatment, the tested respiratory function outcomes in study group still remained significantly better than in control group ($p < 0.05$; Table II).

Biochemical Outcomes

The levels of Cr and lactic acid did not change significantly after the treatment in the study group (Table III). In contrast, the levels of these biochemical parameters significantly increased in the control group 72 hours after the treatment (Table III). While BUN and ALT levels significantly decreased in both groups, the extent of this decrease was smaller in the

Table II. Respiratory function outcomes.

Groups	Time	PaO_2 (mm Hg)	PaO_2/FiO_2	(A-a) DO_2 (kPa)	Qs/Qt (%)	R (times/min)
Study group	Before treatment	93.18 ± 6.37	163.81 ± 11.96	35.17 ± 6.49	42.91 ± 3.86	30.14 ± 1.29
	24 hours after treatment	117.29 ± 5.58*	252.93 ± 12.76*	26.31 ± 2.33*	29.10 ± 3.57*	26.91 ± 1.33*
	48 hours after treatment	139.41 ± 10.62*	294.63 ± 10.47*	23.96 ± 2.58*	26.13 ± 3.62*	24.26 ± 1.83*
	72 hours after treatment	147.26 ± 11.85*	301.75 ± 39.31*	24.80 ± 2.56*	25.09 ± 3.58*	24.10 ± 1.75*
Control group	Before treatment	92.96 ± 5.58	162.59 ± 10.61	34.96 ± 7.72	43.04 ± 3.52	30.29 ± 1.58
	24 hours after treatment	103.69 ± 5.62$^{*\#}$	170.81 ± 10.26$^{\#}$	34.16 ± 7.80$^{\#}$	42.19 ± 3.34$^{\#}$	29.64 ± 1.53$^{\#}$
	48 hours after treatment	117.29 ± 10.80$^{*\#}$	184.91 ± 10.85$^{*\#}$	31.92 ± 2.33$^{*\#}$	39.57 ± 4.26$^{*\#}$	28.31 ± 1.08$^{*\#}$
	72 hours after treatment	119.38 ± 10.23$^{*\#}$	220.96 ± 38.57$^{*\#}$	30.31 ± 2.64$^{*\#}$	37.62 ± 4.14$^{*\#}$	27.81 ± 2.04$^{*\#}$

Footnote: Data are mean ± SEM. PaO_2: arterial oxygen tension, PaO_2/FiO_2: oxygenation index, (A-a) DO_2: alveolar-arterial oxygen difference, Qs/Qt: intrapulmonary arteriovenous shunt percentage, and R: respiratory rate. $^{*}p < 0.05$ *vs.* before treatment; $^{\#}p < 0.05$ *vs.* study group.

Table III. Biochemical outcomes.

Groups	Time point	Cr (μmol/L)	BUN (mmol/L)	ALT (U/L)	Lactic acid (mmol/L)
Study group	Before treatment	126.30 ± 16.54	7.31 ± 1.16	46.71 ± 2.54	1.73 ± 0.38
	72 hours after treatment	152.59 ± 12.14	16.31 ± 1.18*	119.87 ± 17.40*	2.31 ± 0.28
Control group	Before treatment	125.57 ± 15.81	7.26 ± 1.74	45.28 ± 2.49	1.69 ± 0.52
	72 hours after treatment	362.19 ± 10.16*#	32.91 ± 2.04*#	120.39 ± 19.58*	5.41 ± 1.36*#

Footnote: Data are mean ± SEM. Cr: creatinine, BUN: blood urea nitrogen, ALT: alanine transaminase. *p <0.05 vs. before treatment; #p < 0.05 vs. study group.

study group compared with control group (p < 0.05; Table III).

Inflammatory Outcomes

Both groups demonstrated significant decreases of CRP and TNF-α levels, as well as increases in the level of IL-10 and the IL-10/TNF-α ratio, after the treatment (Table IV). However, these changes were more pronounced in the study group (p < 0.05 *vs.* control group; Table IV).

Prognostic Outcomes

The MODS and APACHE II scores in both groups significantly decreased after the treatment, and the extent of these changes was more pronounced in study group (p < 0.05 *vs.* control group; Table V).

All patients in both groups survived, and there were no differences in the use of mechanical ventilation (Table VI). The occurrence rates of MODS and ARDS were significantly lower in the study group compared with control group (p < 0.05; Table VI).

Discussion

SAP is accompanied by a systemic inflammatory response syndrome which leads to a massive release of inflammatory mediators in the body, affecting the organs near and far away from the pancreas[10]. This inflammatory response is the principal cause of ALI which is often accompanied by pulmonary interstitial oedema and severe hypoxemia. These respiratory disorders can induce ARDS or severe MODS, which are life-threatening[11]. Continuous blood filtration can restore homeostasis and improve immune function by removing excess cytokines from the body. This therapy has been widely used in the treatment of sepsis and systemic inflammatory response syndrome. However, therapeutic benefits of continuous blood filtration in SAP were not obvious[12]. To further examine this, we evaluated the usefulness of early blood filtration in SAP complicated by ALI.

We observed that patients treated with early blood filtration therapy, administered in addition to routine treatment, showed a significant improvement of respiratory function outcomes as early as 24 hours after the treatment. Similar changes were observed in control group (routine treatment only) only after 48 hours after the treatment. Even despite positive outcome trends in the control group, the parameters did not reach the levels seen in the study group after 72 hours after the treatment, indicating that improvement of respiratory function proceeded in the control group slower than the study group. This demonstrated beneficial effects of early blood purification

Table IV. Inflammatory outcomes.

Groups	Time point	CRP (mg/L)	TNF-α (ng/mL)	IL-10 (pg/mL)	IL-10/TNF-α
Study group	Before treatment	29.81 ± 7.06	60.59 ± 8.33	54.17 ± 8.26	0.90 ± 0.25
	72 hours after treatment	20.38 ± 5.24*	41.70 ± 7.62*	50.03 ± 7.58*	1.18 ± 0.23*
Control group	Before treatment	28.93 ± 7.24	60.31 ± 8.57	53.95 ± 8.55	0.91 ± 0.24
	72 hours after treatment	24.36 ± 5.26*#	52.08 ± 6.44*#	50.81 ± 7.62*	1.02 ± 0.31*#

Footnote: Data are mean ± SEM. **p <0.05 vs. before treatment; #p < 0.05 vs. study group.

Table V. MODS and APACHE II scores.

Groups	Time point	MODS score	APACHE II score
Study group	Before treatment	8.96 ± 2.25	20.37 ± 4.58
	72 hours after treatment	4.17 ± 1.62*	8.20 ± 1.53*
Control group	Before treatment	8.87 ± 2.61	20.61 ± 3.58
	72 hours after treatment	5.39 ± 1.75*#	11.36 ± 4.29*#

Footnote: Data are mean ± SEM. MODS: multiple organ dysfunction syndrome. *$p < 0.05$ vs. before treatment; #$p < 0.05$ vs. study group.

therapy on respiratory function in patients with SAP complicated by ALI. Because of better improvement of respiratory function, the occurrence of ARDS and MODS has been better controlled in study group, which has important implications for rehabilitation and improving prognosis in these patients.

As medical technology and auxiliary equipment continue to develop, mortality from SAP is better controlled than before[13]. Thus, in our study, survival rates in both patient groups reached 100% regardless of the occurrence of MODS or ARDS. This confirms that treatment of SAP complicated by ALI is an important prerequisite to ensure patients' survival.

We further studied systemic inflammatory cytokine response in these patients. Specifically, we evaluated blood levels of TNF-α and IL-10. The former is an important pro-inflammatory cytokine, promoting the development of SAP by up-regulating production of other inflammatory mediators. The latter is an anti-inflammatory cytokine with a strong immunosuppressing function. It plays an important role in inhibiting activation of TNF-α and down-regulating excessive immune responses. In this study, changes in CRP, the systemic inflammatory marker, and TNF-α and IL-10 levels, as well as IL-10/TNF-α ratio, were more advantageous in the study group, highlighting the favorable effect of early blood filtration therapy on clearing inflammatory mediators and improving immune function in these patients. Some authors believe that substantial liquid input in patients with SAP often causes extravascular pulmonary oedema which cannot be effectively mitigated[14]. Then, the application of early blood filtration therapy can improve blood colloid osmotic pressure, playing an important role in dehydration, which is beneficial for relieving pulmonary oedema and improving pulmonary function[15]. In addition, early blood filtration therapy can quickly remove the excess of heat generated within the body during SAP, thereby promoting recovery of bodily temperature and decrease of basal metabolic rate[16-18]. This improves systemic oxygen consumption, relieves tachycardia, tachypnoea and other symptoms caused by the increase in oxygen consumption. Therefore, SAP complicated by ALI benefits from early blood purification, and the sooner this therapy is carried out, the better is the relief of patients' clinical symptoms.

Some authors believe that ALI and ARDS are, in fact, manifestations of MODS in the lung. In turn, development of ALI and ARDS further aggravates the failure of other organs[19,20]. Therefore, when early blood purification therapy promotes recovery of respiratory function and improves immune homeostasis, MODS and APACHE II scores are decreased, and physical condition is gradually improved. It should be noted that effective circulating blood volume is often low in patients with SAP, and excessive heat removed by early blood purification therapy may lead to metabolic acidosis and coagulopathy[21]. Therefore, one needs to pay close attention to supplementing

Table VI. Prognostic outcomes,

Groups	Mechanical ventilation	MODS	ARDS	Mortality
Study group	12 (37.5)	6 (18.8)	2 (6.3)	0
Control group	15 (46.9)	11 (34.3)	6 (18.8)	0
p	n.s.	< 0.05	< 0.05	n.s.

Footnote: Data are absolute numbers (%). MODS: multiple organ dysfunction syndrome; ARDS: acute respiratory distress syndrome. n.s.: not significant.

albumin and plasma, and to making precautionary measures and monitoring coagulation in order to ensure the safety of the therapy.

Conclusions

Early blood purification therapy improves respiratory function and inflammatory cytokine levels in patients with SAP complicated by ALI, and decreases the occurrence of MODS and ARDS.

Conflict of Interests

The Authors declare that they have no conflict of interests.

References

1) Bishehsari F, Sharma A, Stello K, Toth C, O'Connell MR, Evans AC, LaRusch J, Muddana V, Papachristou GI, Whitcomb DC. TNF-alpha gene (TNFA) variants increase risk for multi-organ dysfunction syndrome (MODS) in acute pancreatitis. Pancreatology 2012; 12: 113-118.
2) Chacko B, Peter JV, Tharyan P, John G, Jeyaseelan L. Pressure-controlled versus volume-controlled ventilation for acute respiratory failure due to acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). Cochrane Database Syst Rev 2015; 1: Cd008807.
3) Luan ZG, Zhang J, Yin XH, Ma XC, Guo RX. Ethyl pyruvate significantly inhibits tumour necrosis factor-alpha, interleukin-1beta and high mobility group box 1 releasing and attenuates sodium taurocholate-induced severe acute pancreatitis associated with acute lung injury. Clin Exp Immunol 2013; 172: 417-426.
4) Jiang CF, Shiau YC, Ng KW, Tan SW. Serum interleukin-6, tumor necrosis factor alpha and C-reactive protein in early prediction of severity of acute pancreatitis. J Chin Med Assoc 2004; 67: 442-446.
5) Luan ZG, Zhang XJ, Yin XH, Ma XC, Zhang H, Zhang C, Guo RX. Downregulation of HMGB1 protects against the development of acute lung injury after severe acute pancreatitis. Immunobiology 2013; 218: 1261-1270.
6) Elder AS, Saccone GT, Dixon DL. Lung injury in acute pancreatitis: mechanisms underlying augmented secondary injury. Pancreatology 2012; 12: 49-56.
7) Liu G, Zhang J, Chen H, Wang C, Qiu Y, Liu Y, Wan J, Guo H. Effects and mechanisms of alveolar type II epithelial cell apoptosis in severe pancreatitis-induced acute lung injury. Exp Ther Med 2014; 7: 565-572.
8) Du XG, Chen XM, Gan H, Li ZR, Wen YJ, Wang XC. Continuous blood purification ameliorates RhoA-mediated endothelial permeability in severe acute pancreatitis patients with lung injury. Int J Artif Organs 2011; 34: 348-356.
9) Akbarshahi H, Rosendahl AH, Westergren-Thorsson G, Andersson R. Acute lung injury in acute pancreatitis--awaiting the big leap. Respir Med 2012; 106: 1199-1210.
10) Wang XY, Tang QQ, Zhang JL, Fang MY, Li YX. Effect of SB203580 on pathologic change of pancreatic tissue and expression of TNF-alpha and IL-1beta in rats with severe acute pancreatitis. Eur Rev Med Pharmacol Sci 2014; 18: 338-343.
11) Buddingh KT, Koudstaal LG, van Santvoort HC, Besselink MG, Timmer R, Rosman C, van Goor H, Nijmeijer RM, Gooszen H, Leuvenink HG, Ploeg RJ, Nieuwenhuijs VB. Early angiopoietin-2 levels after onset predict the advent of severe pancreatitis, multiple organ failure, and infectious complications in patients with acute pancreatitis. J Am Coll Surg 2014; 218: 26-32.
12) Yubero S, Manso MA, Ramudo L, Vicente S, De Dios I. Dexamethasone down-regulates the inflammatory mediators but fails to reduce the tissue injury in the lung of acute pancreatitis rat models. Pulm Pharmacol Ther 2012; 25: 319-324.
13) Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol 2013; 108: 1400-1415; 1416.
14) Malmstrom ML, Hansen MB, Andersen AM, Ersboll AK, Nielsen OH, Jorgensen LN, Novovic S. Cytokines and organ failure in acute pancreatitis: inflammatory response in acute pancreatitis. Pancreas 2012; 41: 271-277.
15) Chu LP, Zhou JJ, Yu YF, Huang Y, Dong WX. Clinical effects of pulse high-volume hemofiltration on severe acute pancreatitis complicated with multiple organ dysfunction syndrome. Ther Apher Dial 2013; 17: 78-83.
16) Gajic O, Dabbagh O, Park PK, Adesanya A, Chang SY, Hou P, Anderson H, 3rd, Hoth JJ, Mikkelsen ME, Gentile NT, Gong MN, Talmor D, Bajwa E, Watkins TR, Festic E, Yilmaz M, Iscimen R, Kaufman DA, Esper AM, Sadikot R, Douglas I, Sevransky J, Malinchoc M. Early identification of patients at risk of acute lung injury: evaluation of lung injury prediction score in a multicenter cohort study. Am J Respir Crit Care Med 2011; 183: 462-470.
17) Su X, Bai C, Hong Q, Zhu D, He L, Wu J, Ding F, Fang X, Matthay MA. Effect of continuous hemofiltration on hemodynamics, lung inflammation and pulmonary edema in a canine model of acute lung injury. Intensive Care Med 2003; 29: 2034-2042.
18) Zhang H, Neuhofer P, Song L, Rabe B, Lesina M, Kurkowski MU, Treiber M, Wartmann T, Regner S, Thorlacius H, Saur D, Weirich G, Yoshimura A, Halangk W, Mizgerd JP, Schmid RM, Rose-John S, Algul H. IL-6 trans-signaling promotes pancreatitis-associated lung injury and lethality. J Clin Invest 2013; 123: 1019-1031.
19) Huai JP, Sun XC, Chen MJ, Jin Y, Ye XH, Wu JS, Huang ZM. Melatonin attenuates acute pancreatitis-associated lung injury in rats by modulating interleukin 22. World J Gastroenterol 2012; 18: 5122-5128.
20) Pang T, Chen W, Lu ZM, Luo TH, Zhou H, Xue XC, Bi JW, Fang GE. Endothelial progenitor cells are influenced by serum of patients with systemic inflammatory response syndrome or multiple organ dysfunction. Eur Rev Med Pharmacol Sci 2013; 17: 3169-3177.
21) Gao Smith F, Perkins GD, Gates S, Young D, McAuley DF, Tunnicliffe W, Khan Z, Lamb SE. Effect of intravenous beta-2 agonist treatment on clinical outcomes in acute respiratory distress syndrome (BALTI-2): a multicentre, randomised controlled trial. Lancet 2012; 379: 229-235.