Early Initiation of Continuous Renal Replacement Therapy Improves Clinical Outcomes in Patients With Acute Respiratory Distress Syndrome

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Abstract: *Background:* The acute respiratory distress syndrome (ARDS) is a common devastating syndrome in intensive care unit in critically ill patients. Continuous renal replacement therapy (CRRT) has been shown beneficial effects on oxygenation and survival in patients with ARDS. However, it is still controversial about the timing of initiation of CRRT. *Methods:* Fifty-three patients with ARDS admitted to intensive care unit in Zhejiang Provincial People's Hospital, China from 2009 to 2013 were enrolled in the study. The authors compared ventilation parameter, including PaO_2/FIO_2, A-a gradient, positive end-expiratory pressure, plateau pressure, dynamic compliance and hemodynamic parameters, including central venous pressure, mean arterial pressure, cardiac index, extravascular lung water index, fluid balance between early initiation (within 12 hours after ARDS onset) and late initiation of CRRT (48 hours after ARDS onset) groups. The authors further investigated transforming growth factor (TGF)-β1 level changes in serum and bronchoalveolar lavage fluid (BALF) by enzyme-linked immunosorbent assay during 7 days of follow-up. *Results:* Significant improvement of oxygenation and shorter duration of mechanical ventilation were observed in early CRRT group during 7-day follow-up. In addition, TGF-β1 concentrations in serum and BALF were significantly decreased in patients with early initiation of CRRT compared to those with late initiation of CRRT on day 2 and day 7. Furthermore, patients who died of ARDS had higher levels of TGF-β1 in BALF than survivors. *Conclusions:* Our findings showed that early initiation of CRRT is associated with favorable clinical outcomes in ARDS patients, which might be due to the reduced serum and BALF TGF-β1 levels through CRRT. However, large multi-center studies are needed to make further recommendations as to the optimal use of CRRT in ARDS patient populations.

Key Indexing Terms: Critically ill; ARDS; CRRT; Cytokines; TGF-β1. **[Am J Med Sci 2015;349(3):199–205.]**

The acute respiratory distress syndrome (ARDS) is a common devastating syndrome in critically ill patients in intensive care unit (ICU) with the mortality as high as 27% to 45%.[1] It is characterized by increased permeability of alveolar-capillary barrier, which is composed of the microvascular endothelium and alveolar epithelium, then further resulting in extravascular accumulation of protein-rich edema fluid, leukocytes and erythrocytes into the alveolar space, as well as production of proinflammatory cytokines, such as tumor necrosis factor-α, interleukin (IL)-1, IL-6, platelet-derived growth factor, etc.[2–4] Clinically, it presents as refractory hypoxemia and noncardiogenic pulmonary edema. Currently, there is no available pharmacological therapy for ARDS and the main treatment is supportive.[2] Measures aimed at reducing fluid overload, inflammation and especially the implementation of lung-protective ventilation strategy have been shown to improve clinical outcomes in patients with ARDS.[1]

Transforming growth factor (TGF)-β1 is a key mediator for developing ARDS. It is activated locally by integrin αvβ6 in cooperation with protease-activated receptor-1[5] to increase epithelial and endothelial permeability and promote alveolar flooding.[6] It is a strong chemoattractant, not only for fibroblasts[7] but also for T cells,[8] macrophages and neutrophils.[9] Moreover, it stimulates the expression of multiple cytokines, including tumor necrosis factor-α, IL-1 and platelet-derived growth factor, and inhibits expression of surfactant.[10] Previous studies have reported a progressive and significant increase of serum TGF-β1 concentrations over time in patients with sepsis-induced ARDS[11] and the elevated levels of TGF-β1 were correlated with decreases in PaO_2/FIO_2 ratio and survival.[12] Furthermore, early studies in animal models have shown that blocking TGF-β with monoclonal antibody prevented hemorrhage-induced acute lung injury[13] and bleomycin-induced lung fibrosis.[14] Therefore, targeting TGF-β1 may represent a beneficial intervention in treating patients with ARDS.

Continuous renal replacement therapy (CRRT) has been extensively used as renal support for critically ill patients in ICU. In recent years, it has also been extended to nonrenal indications, including sepsis, multiple organ dysfunction syndrome, congestive heart failure, ARDS, etc.[15–19] Although CRRT has not been included in the standard therapy for ARDS, multiple studies have demonstrated that CRRT could improve survival in patients with ARDS due to different etiologies.[20–25] However, it is still controversial about the timing of initiation of CRRT, which might exert significant influence on clinical outcomes. The current study, as a pilot project, aims to compare the effects of the timing of initiation of CRRT on clinical outcomes in patients with ARDS and to further investigate the changes of TGF-β1 levels in those patients.

MATERIALS AND METHODS

Study Patients Selection

Fifty-three patients aged between 25 and 65 years admitted to the ICU at Zhejiang Provincial People's Hospital, China from March 2009 to March 2013 and who met the 1994 American-European Consensus definition for ARDS[26] were enrolled in the study. Informed consent was obtained from patients or surrogates. The protocol was approved by the institutional review board of the hospital. Patients were excluded if they had immunodeficiency, autoimmune disease or cancer or

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Submitted April 15, 2014; accepted in revised form October 6, 2014.

Supported by the Grants from Science and Technology Department of Zhejiang Province, China (2011R50018-14) and Zhejiang Provincial Health Department, China (2012KYB021 and 2013RCA004).

The authors have no conflicts of interest to disclose.

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were under any form of immunomodulating treatment. Patients were admitted to ICU once they were diagnosed with ARDS and were randomly assigned to early initiation of CRRT (within 12 hours of ICU admission) group or late initiation of CRRT (after 48 hour of ICU admission) group. Twenty healthy individuals matched for age and sex served as control group.

Mechanical Ventilation

All patients meeting ARDS criteria were ventilated with low tidal volumes (VT) of 6 mL/kg predicted body weight, inspiratory plateau pressure limited at 30 $cm \cdot H_2O$, initial ventilator rate of 30 breaths per minute adjusted to maintain a pH goal of 7.30 to 7.45, fraction of inspired oxygen (FIO_2) ensuring PaO_2 >60 mm Hg and positive end-expiratory pressure (PEEP) level that permitted the best oxygenation with lowest FIO_2 without adverse hemodynamic effects. Patients were weaned and extubated according to the standard protocol described in the ARDSNet study.[27]

Continuous Renal Replacement Therapy

The Aquarius system and Fresenius V600S polysulfone membrane hemofilters were used to deliver CRRT. The ultrafiltrate was removed at a rate of 250 mL/hr, blood flow was 150 to 200 mL/min. Heparin was used for anticoagulation of the circuit in patients without coagulopathy. Replacement solutions consist of Na^+ 147 mmol/L, Cl^- 115 mmol/L, HCO_3^- 76 mmol/L, $Ca2^+$ 2.4 mmol/L, $Mg2^+$ 0.7 mmol/L and Glu 200 mg/L. K^+ was adjusted accordingly.

Clinical Data Collection

All patients were closely monitored from day 0 to day 7. Ventilator parameters, including PaO_2, FIO_2, VT, peak inspiratory pressure, PEEP, plateau pressure, etc, were recorded. PaO_2/FIO_2 ratio and dynamic compliance (Cdyn) [VT/(peak inspiratory pressure − PEEP)] were calculated. Extravascular lung water index (EVLWI) was measured at the bedside using the PiCCO (Pulsion, Munich, Germany). Cardiac index is expressed in liters per minutes to body surface area ($L \cdot min^{-1} \cdot m^{-2}$). Mortality was defined as death occurring within 28 days after the patients' enrollment.

Specimen Collection

All patients were intubated at the time of bronchoalveolar lavage (BAL). BAL was performed on days 0 (baseline), 2 and 7 of follow-up. The bronchoalveolar lavage fluid (BALF) was spun at 3,000 rpm for 10 minutes and the supernatant was obtained for TGF-β1 detection.

Blood samples were drawn using an indwelling arterial catheter into sterilized, silicone-coated tubes at the time of ARDS diagnosis on days 0, 2 and 7 thereafter. Blood samples were collected in parallel from the healthy blood donors used as controls. Serum samples were obtained from clotted whole blood and frozen at −70°C for TGF-β1 detection.

TGF-β1 Detection

TGF-β1 concentrations in BALF and serum were determined by enzyme-linked immunosorbent assay kit purchased from Wuhan Boster Biological Engineering Co., Ltd. (Wuhan, China) according to the manufacturer's instructions.

Statistics

All data are presented as mean ± standard deviation. Descriptive statistics were computed to describe the demographic and clinical variables. Statistical analyses for differences between group means were conducted by unpaired Student's *t* test. $P < 0.05$ was considered statistically significant. SPSS 13.0 software (SPSS, Chicago, IL) and PRISM 5.0 (GraphPad Software, Inc., La Jolla, CA) were used to analyze the data.

RESULTS

Patient Characteristics

In the present study, the baseline patient characteristics are shown in Table 1. We analyzed a total number of 53 patients with ARDS who fulfilled the diagnostic criteria. All patients were treated according to the low-tidal-volume strategy previously reported.[27] The mean age in patients with early CRRT was 50.36 years and 70.4% (19/27) was male while the mean age in patients with late CRRT was 53.12 years and 65.4% (17/26) was male. The mean age in healthy control group was 46.79 years and 70% was male. There were no differences in age and gender between 2 groups. Sepsis was the major cause of ARDS in 2 groups (40.7% and 38.5%, respectively). Other causes of ARDS included pneumonia, polytrauma, stroke and aspiration. Among the study subjects, 11.3% (3/27) in the early CRRT group and 7.7% (2/26) in the late CRRT group had increased creatinine levels. The average initial creatinine levels were 1.02 ± 0.31 mg/dL and 0.94 ± 0.34 mg/dL in the early CRRT and late CRRT group, respectively, which did not show a significant difference.

Clinical Outcomes of the Study Patients

As showed in Table 2, there were no significant differences in PaO_2/FIO_2, PEEP, plateau pressure and A-a gradient in patients between early CRRT and late CRRT at baseline of day 0. However, the trends of steady improvement of these parameters were observed in both groups over the 7 days of follow-up. There were significant improvements in PaO_2/FIO_2 at day 7, and PEEP and A-a gradient at days 4 and 7 in early CRRT group compared with late CRRT group.

We further evaluated the effects of CRRT on Cdyn. Consistent with the changes of PaO_2/FIO_2, we observed similar trends of steady increase of Cdyn between early and late initiation of CRRT patients among 7 days of follow-up. On day 7 of follow-up, there was significant higher Cdyn in patients with early

TABLE 1. Subjects' characteristics and clinical features

	Early CRRT	Late CRRT	Control	*P*
Patients	27	26	20	—
Age	50.36 ± 16.97	53.12 ± 15.05	46.79 ± 18.92	—
Gender (M/F)	19/8	17/9	14/6	—
Causes of ARDS				
Sepsis	40.7% (11)	38.5% (10)	—	0.86533
Pneumonia	18.5% (5)	23.1% (6)	—	0.68249
Polytrauma	18.5% (5)	15.4% (4)	—	0.95046
Stroke	14.8% (4)	15.4% (4)	—	0.95726
Aspiration	7.4% (2)	15.4% (4)	—	0.96463
AKI patient number	11.1% (3)	7.7% (2)	—	—
Creatinine (mg/dL)	1.02 ± 0.31	0.94 ± 0.34	—	0.35180

ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; CRRT, continuous renal replacement therapy; F, female; M, male.