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Early Clinical Efficacy of Prone Ventilation in Patients with Connective Tissue Disease-Related Interstitial Lung Disease with Concurrent Acute Respiratory Distress Syndrome

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Abstract: In this prospective study, we aimed to compare the early (4h) clinical responses of prone conventional ventilation (CV) in connective tissue disease-related interstitial lung disease (CTD-ILD) patients with concurrent acute respiratory distress syndrome (ARDS). 40 patients with CTD-ILD combined with early onset of ARDS were recruited from May 2021 to March 2022 in the First Hospital of Jinmen, China. They were separated into two groups (n=20 per group). Patients in the control group were given routine treatment, which included infection control, correcting electrolyte disorder, correcting the acid-base imbalance, and nutritional support, etc. For the intervention group, additional conventional ventilation in the prone position (prone-CV) was provided. The following indicators were monitored, including respiratory rate (RR), heart rate (HR), mean arterial pressure (MAP) and central venous pressure (CVP). The changes in sequential organ failure assessment score (SOFA), respiratory dynamic indexes (RR and PaO_2/FIO_2) and hemodynamics, including HR, CVP (mm Hg) and MAP (mmHg) were compared before and 4 hours after treatment. After 4 h of treatment, patients in the prone-CV group had significantly lowered SOFA scores (9.134 ± 1.12 vs. 10.03 ± 0.84, $p = 0.007$) and improved PaO_2/FIO_2 ratio (184.8 ± 35.59 vs. 104.2 ± 14.64, $p < 0.001$) compared to the control group. The hemodynamics, including HR, MAP and CVP were stable. In conclusion, early administration of Prone-CV could rapidly improve the SOFA score and oxygenation among CTD-ILD patients during acute exacerbations of ARDS.

Keywords: CTD, ILD, Prone-CV, Oxygenation

1. Introduction

Connective tissue diseases (CTDs) are a group of autoimmune diseases with similar chronic noninfectious inflammation of systemic blood vessels and connective tissues at a variety of sites in the body [1, 2]. Interstitial lung disease (ILD) is developed when the blood vessels and connective tissues of the lung suffer damage [3, 4]. CTD-ILD is characterized by inflammation and fibrosis of the lung [1], leading to pathological alterations and functional loss of the alveolar wall, alveolar cavity, adjacent small vessels and trachea [3, 5]. These changes increase the permeability of the alveolar epithelium and vascular endothelium. With the progress of the disease, all patients develop some degree of respiratory failure. The clinical manifestations include dyspnea and extensive infiltrating shadow in the chest, resulting in significant morbidity and mortality [3, 5, 6].

Patients with CTD-ILD can develop acute respiratory distress syndrome (ARDS) due to an exacerbation of the underlying disease [7, 8]. At present, the main management for ARDS is still based on respiratory support technologies, aiming to alleviate intractable hypoxia, elevate blood pressure, prevent alveolar collapse, reduce the degree of pulmonary edema and improve oxygen and reduce ventilator fatigue. The major auxiliary ventilation therapies include 1, small tidal volume and low platform pressure ventilation; 2, positive end-expiratory pressure (PEEP); 3, conventional ventilation in the prone position (prone-CV); 4, high-frequency oscillatory ventilation (HFOV); 5, extracorporeal membrane oxygenation (ECMO); and 6, noninvasive ventilation (NIV). The principles for ventilation strategy selection include lung protection and step-by-step utilization of complex invasive interventions [9]. However, patients diagnosed with ARDS have varying underlying diseases, leading to complex premorbid and comorbid conditions [9].

A series of previous studies demonstrated that prone-CV could improve oxygenation, reduce pulmonary vascular resistance and reduce right ventricular afterload [10-12]. Prone-CV also increases abdominal pressure, which further contributes to the increase of blood circulation and the preload and afterload of the heart [10-12]. Early lung protective prone ventilation can effectively reduce the mortality of patients with ARDS [10-12]. In patients with acute exacerbations of ILD, prone-CV improves oxygenation and partially improves hemodynamic parameters [9, 13]. However, patients with hydrostatic pulmonary edema (lung fibrotic features similar to ILD) and late ARDS, might not respond to prone-CV [14]. Therefore, we hypothesized that prone-CV should be provided as early as possible for patients with acute exacerbations of ILD. To validate this hypothesis, we conducted a prospective study to assess the early (4h) clinical efficacy of prone-CV in CTD-ILD patients with acute exacerbations of ARDS.

2. Methods

2.1. Inclusion and Exclusion Criteria

40 patients with CTD-ILD combined with early onset of ARDS and meeting the following inclusion criteria were recruited from May 2021 to March 2022. This study was approved by the Ethics Committee of Jingmen No. 1 People's Hospital, China (Approval no. 202102070). Informed consent was obtained from all participants. According to their willingness, patients were divided into the intervention or control groups, with 20 cases in each group. The following criteria were applied: 1. Patients diagnosed with CTD-ILD; 2. Oxygenation index (PaO_2/FiO_2) <200 mmHg. The following exclusion criteria were applied: 1. The patients have other serious organic diseases; 2. Patients with active hemorrhage or pneumothorax; 3. Mental abnormality or blurred consciousness; 4. Pregnant or lactating women.

2.2. Ventilation

Patients in the control group were given routine treatment, which included infection control, correcting electrolyte disorder, correcting the acid-base imbalance, and nutritional support, etc. For the intervention group, additional conventional ventilation in the prone position (prone-CV) was provided by using the following operations:

1. Four medical staff assist the patient in taking the lateral lying position and then turning to the prone position after the vital signs are stable. Then, they use a cushion to pad the iliac and shoulders, fix the head with the head ring, and keep the upper limbs in a semi-curved state. The lower limbs are naturally separated, and the hands are naturally placed upward;
2. When the patient turns over, the medical staff needs to check the tracheotomy cannula and endotracheal intubation, connection of ventilator, observe the change of airway pressure, and fix the intravenous infusion pipe and drainage pipe in time. If the patients are restless during the prone position, they must be constrained with a restraint belt.
3. After sufficient sedation, mechanical ventilation is carried out by Mindray Ventilator (SV300). Synchronous intermittent command ventilation mode is adopted. The tidal volume is controlled at 6-8ml/kg. The following parameters were adopted, breathing rate: 14-20 times/min, the inspiration time: 1.0-1.2s, the peak flow rate: 45-50L/min, the inhaled oxygen concentration: 40%-100%, and the ventilation time: 4h.
4. Prone ventilation therapy is stopped when the patient's $PaO_2/FiO_2 \geq 200$mmHg or cannot tolerate it.

2.3. Observational Index and Statistical Analysis

The following indicators were monitored, including respiratory rate (RR), heart rate (HR), mean arterial pressure (MAP) and central venous pressure (CVP). The changes in sequential organ failure assessment score (SOFA), respiratory dynamic indexes (RR and PaO_2/FIO_2) and hemodynamics, including HR, CVP (mm Hg) and MAP (mmHg) were compared before and 4 hours after treatment.

GraphPad Prism 8.1.0 statistical software was used for data analysis. The measurement data were measured by mean ± standard deviation (SD). Independent sample t-test was used for inter-group comparison, and paired t-test was used for intra-group comparison. $p<0.05$ was statistically significant.

3. Results

3.1. Comparison of the Baseline Demographic and Clinical Characteristics in CTD-ILD Concurrent with ARDS Patients Enrolled in This Study

In this study, 40 patients with CTD-ILD concurrent with ARDS were recruited. They were divided into the control (n=20, female=12, male=8) and prone-CV (n=20, female=12, male=8) groups according to their willingness. Their baseline demographic and clinical characteristics are summarized in Table 1. The age was 59.1±8.33 and 58.85±7.75 and the body weight (kg) was 58.89±8.14 and 61.88±9.96, respectively in the two groups. Group comparisons did not find statistically significant differences between the control and intervention groups in terms of the SOFA score, PaO_2/FIO_2 ratio, respiratory rate, heart rate, mean arterial pressure, and central venous pressure (Table 1).

***Table 1.** Baseline and clinical characteristics of patients enrolled in this study.*

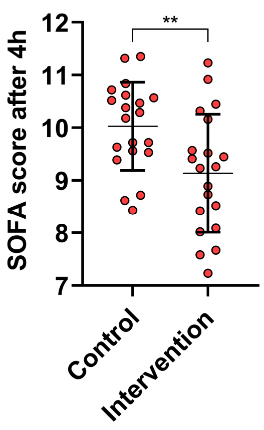
Clinical characteristics	Control (n=20)	Prone-CV (n=20)	*p* value
Age (mean ± SD)	59.1±8.33	58.85±7.75	0.92
Gender (Male/Female)	8/12	8/12	1.00
Weight (kg, mean ± SD)	58.89±8.14	61.88±9.96	0.31
SOFA score before study	10.15±1.00	10.06±1.22	0.80
PaO_2/FIO_2 ratio before study, mm Hg	99.20±15.82	100.8±15.72	0.75
Respiratory rate before study	24.20±1.88	24.55±2.14	0.59
Heart rate (bpm) before study	107.4±10.39	104.65±9.37	0.39
Mean arterial pressure (mmHg) before study	88.85±6.62	88.15±7.71	0.75
Central venous pressure (mmHg) before study	88.85±6.62	88.15±7.71	0.19

3.2. Comparison of Oxygenation Variables

After 4 h of therapy, the prone-CV group had a significantly lower SOFA score than the control group (9.134±1.12 vs. 10.03±0.84, p=0.007) (Figure 1). Prone-CV treatment significantly improved PaO_2/FIO_2 ratio (from 100.8±15.72 to 184.8±35.59, p<0.001). However, such improvement was not observed in the control group (from 99.20±15.82 to 104.2±14.64, p=0.31). Therefore, we observed a significantly higher PaO_2/FIO_2 ratio in the Prone-CV group compared to the control after 4 h of treatment (Figure 2A, p<0.001). In contrast, there is no significant difference in respiratory rate (Figure 2B, p=0.67).

3.3. Comparison of Hemodynamics

Compared to the baseline data, the heart rate was lower in the control (107.4±10.39 vs. 101.0±8.40, p=0.037) and prone-CV group (104.65±9.37 vs. 96.75±6.62, p=0.004) after 4 h of treatment. However, no significant difference was observed between the two groups after 4 h of treatment (Figure 3A, p=0.09). In comparison, MAP and CVP remain changed in both control and prone-CV groups during the 4 h of treatment. Therefore, there was no significant difference in CVP or MAP between the control and prone-CV groups after 4 h of treatment (Figure 3B-C, p=0.60 and 0.097, respectively).



**, p<0.01.

***Figure 1.** Comparison of SOFA score between control and prone-CV groups after 4 h of treatment.*

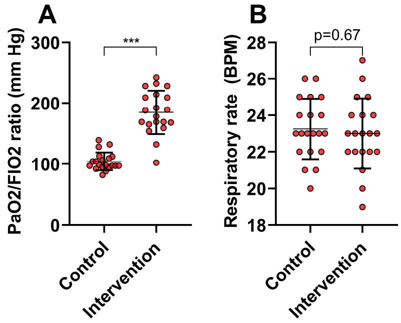


***Figure 2.** Comparison of oxygenation variables between control and prone-CV groups after 4 h of treatment.*

A-B. Comparison of PaO_2/FIO_2 ratio (A) and respiratory rate (B) between the control and prone-CV groups after 4 h of treatment. **, p<0.01. ***, p<0.001.

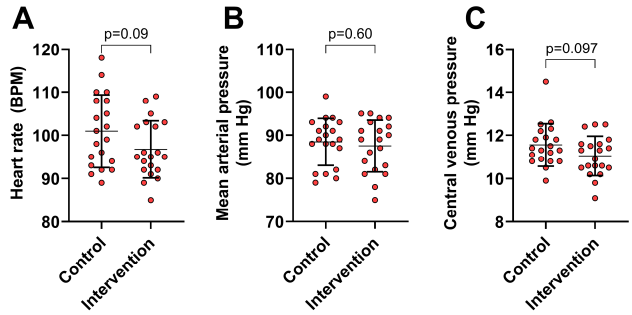


***Figure 3.** Comparison of hemodynamics between control and prone-CV groups after 4 h of treatment.*

A-C. Comparison of heart rate (A), mean arterial pressure (B) and central venous pressure (C) between the control and prone-CV groups after 4 h of treatment.

4. Discussion

In patients with CTD-ILD, early symptoms are not obvious and the disease develops slowly. However, when the patients develop ARDS, the mortality rate increase sharply. Therefore, early mechanical ventilation is of great significance for treating the disease. Currently, there are no exact evidence-based guidelines for the treatment of CTD-ILD. Some scholars have proposed that immunosuppressive treatment is needed when high-resolution CT confirms more than 20% of interstitial abnormalities [15]. When the degree of pulmonary fibrosis cannot be determined, lung function should be assessed and used for making a therapeutic decision. However, some studies reported that the lung function of systemic sclerosis-ILD patients with FVC>50% decreases only slightly without treatment [16]. Therefore, we infer that regardless of the stage of the disease, CTD-ILD should be treated as early as possible when there is continuous disease progression [17].

In the past decades, some ventilation strategies have been tested for CTD-ILD associated with ARDS, but their limitations are quite evident. For example, since HFOV uses very low tidal volumes and high frequencies to achieve ventilation, it might be a potentially ideal mode to avoid ventilator-induced lung injury (VILI) [18]. In patients with refractory hypoxemia, HFOV can significantly improve oxygenation and reduce the rate of refractory hypoxemia [18]. However, in patients with mild-moderate ARDS, HFOV might be associated with increased mortality due to worsened volutrauma and impaired hemodynamics [18]. Since prone-CV has known efficiency in improving oxygenation and hemodynamic parameters in patients with CTD-ILD [13], we focused on this ventilation technique.

In the current study, we recruited 40 CTD-ILD patients with concurrent ARDS and assigned them into two groups according to their willingness. Their baseline demographic and clinical characteristics are similar before the interventions. After 4 h of treatment, patients in the prone-CV group had significantly lowered SOFA scores (9.134 ±1.12 vs. 10.03±0.84, p=0.007) and improved PaO_2/FIO_2 ratio (184.8±35.59 vs. 104.2±14.64, p<0.001) compared to the control group. The hemodynamics, including heart rate, mean arterial pressure and central venous pressure were stable. The present study completely supports the conclusions of one previous retrospective study, which indicated that prone-CV could improve oxygenation during acute exacerbations of ILD [13].

This study also has some limitations. Firstly, the duration of the intervention is relatively short. Only data after 4 h intervention was collected. The long-term survival data and blood cytokines and cytology are supposed to be collected for a better understanding of the development of the disease. Secondly, the sample size is relatively small. Since this is a preliminary study, a further study based on a larger sample size should be conducted.

5. Conclusion

Patients who received early administration of prone-CV had significantly lower SOFA scores and improved PaO_2/FIO_2 ratio compared to their counterparts in the control group. Their hemodynamics, including heart rate, mean arterial pressure and central venous pressure were stable. Therefore, we infer that this strategy is safe and clinically efficient in the early stages of ARDS among patients with CTD-ILD.

Conflict of Interest

The authors have no conflict of interest.

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