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ORIGINAL RESEARCH

Efficacy observation of erythropoietin on sepsis complicated with acute respiratory distress syndrome

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Abstract

This study is to evaluate the efficacy of erythropoietin in treating sepsis-associated acute respiratory distress syndrome (ARDS). One hundred patients with sepsis-related ARDS were randomized into the placebo group and Erythropoietin (EPO) group. Patients in the placebo group received saline as placebo on the standard therapy, while the EPO group received recombinant human erythropoietin injections on the standard therapy. It was found that the heart rate and mean arterial pressure did not differ significantly between days 7 and 14 after treatment initiation ($p > 0.05$). The partial pressure of oxygen (PaO_2) and oxygenation index levels measured on days 7 and 14 were significantly higher than the placebo group and partial pressure of carbon dioxide ($PaCO_2$) was significantly lower than the placebo group ($p < 0.05$). Lung capacity and functional residual capacity (and FRC) increased significantly in tumor necrosis factor-α (TNF-α), interleukin-10 (IL-10), and C-reactive protein (CRP) concentrations ($p < 0.05$). In the EPO group, the duration of mechanical ventilation was significantly shorter and the mortality rate was significantly reduced (Log-Rank test, $\chi^2 = 4.651$, $p = 0.031$). The results confirm that EPO significantly improves lung function and blood gas parameters, reduces serum levels of inflammatory markers, and reduces the risk of death in sepsis-induced ARDS patients, highlighting the potential therapeutic role of EPO in the management of this disease.

Keywords

Erythropoietin; Sepsis; Acute respiratory distress syndrome; Efficacy

1. Introduction

Sepsis is a complex syndrome characterized by an excessive immune response to infection, leading to numerous life-threatening complications. Among these, acute respiratory distress syndrome (ARDS) is one of the earliest and most prevalent complications, particularly when induced by sepsis, characterized by its rapid onset and high mortality rates [1, 2]. Although the pathogenesis of ARDS remains partially understood, it is commonly attributed to diffuse pulmonary vascular endothelial damage and increased vascular permeability, resulting in pulmonary edema and infiltration of inflammatory cells within the lung tissue. Clinically, ARDS manifests as refractory hypoxemia and respiratory distress [3]. Current therapeutic strategies for ARDS, especially when secondary to sepsis, involve supportive care such as respiratory support, antibiotic therapy, anticoagulation and the administration of vasoactive drugs, and till present, there is a lack of specific targeted pharmacological interventions for these patients [4].

Erythropoietin (EPO), a cytokine belonging to the type I cytokine superfamily, exhibits a broad spectrum of tissue-protective effects, including anti-apoptotic, anti-inflammatory, and immunomodulatory actions [5]. Clinically, EPO is extensively used for treating renal anemia and has been shown to enhance cardiac function in heart failure patients [6–8]. Notably, EPO has demonstrated protective effects on lung tissue post-cardiopulmonary resuscitation [9]. Despite these findings, the application of EPO in the treatment of ARDS, particularly sepsis-induced ARDS, has been scarcely reported.

In this study, we explore the potential therapeutic role of EPO in treating patients with sepsis-associated ARDS to provide clinical insights for improving the management of these patients.

2. Research materials and methods

2.1 General data

The data of patients diagnosed with sepsis and ARDS admitted to the Intensive Care Unit of Shaw Hospital affiliated with Nanjing Medical University between March 2021 and March 2023 were retrieved and assessed. The study inclusion criteria for patient selection were a clinical diagnosis for sepsis and ARDS according to the Berlin criteria [10, 11], 18 years or older, received ventilator support and blood purification treatments, had high compliance and complete follow-up clinical

data. Additionally, participants were required to be informed about the study details and to voluntarily sign the informed consent form. The exclusion criteria eliminated patients with cardiogenic shock, concurrent fungal or viral infections (other than those studied), severe gastrointestinal, liver, or kidney failure, coagulopathy, malignant tumors, hemodynamic instability, inability to maintain blood pressure with vasoactive drugs, and immune system deficiencies.

Following the study's enrollment criteria, 100 patients were selected and randomly divided into two groups, each comprising 50 patients, using a random number table based on the order of patient admission.

2.2 Treatment methods

In this interventional study, the patients were stratified into two cohorts: a placebo group and an EPO group. All participants received the standard treatment regimen for sepsis, which comprised fluid resuscitation, antimicrobial therapy, administration of vasoactive agents, anticoagulation therapy, mechanical ventilation, and blood purification treatment.

The placebo group was administered an intravenous infusion of normal saline at a rate of 10 mL/h, adjunct to lung protective ventilation therapy. The evaluation of lung injury severity was conducted after 7 and 14 days of treatment. Concurrently, the EPO group, while also receiving lung protective ventilation, was administered an intravenous injection of EPO (recombinant human erythropoietin injection; Kexing Biopharmaceutical Co., Ltd., approval number S20030089, Jinan, China) at a dose ranging 50–100 U/kg, administered 2–3 times per week, with the option for either intravenous or subcutaneous administration.

2.3 Outcome measures

2.3.1 General data collected

The demographic data, including the mean age and sex distribution of the participants, were recorded. Peripheral venous blood samples were collected within the first 24 hours following admission. After centrifugation, the supernatant was stored in plastic centrifuge tubes at −80 ℃. Laboratory analyses were conducted to determine the peripheral blood white blood cell count (WBC), neutrophil ratio, platelet count, hemoglobin levels, total bilirubin (TBIL), albumin, creatinine (Cr), urea nitrogen, and procalcitonin (PCT) levels. Furthermore, the severity of each patient's condition was evaluated using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score and the Sepsis-Related Organ Failure Assessment (SOFA) score.

2.3.2 Hemodynamic parameters

Heart rate and mean arterial pressure were monitored using a pulse indicator continuous cardiac output (PiCCO) system prior to the initiation of treatment, as well as on the 7th and 14th days post-treatment commencement in both groups.

2.3.3 Comparison of blood gas analysis indicators

The partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$) and oxygenation index of the two groups were observed and statistically compared before treatment and on the 7th and 14th day of treatment.

2.3.4 Comparison of pulmonary volume function indicators

A Computed Tomography (CT) plain scan analysis method was used to scan and collect image data, which was then automatically transferred to the sub-operating console of the CT machine. A calculation software package was used to manually segment each layer and perform cumulative volume calculation and analysis to determine the end-expiratory lung volume (EELV) and functional residual capacity (FRC) at various time points.

2.3.5 Inflammatory factor levels

Before enrollment and on the mornings of the 7th and 14th days of treatment, fasting blood samples were collected from the cubital vein of the patients. Serum levels of tumor necrosis factor-α (TNF-α), interleukin-10 (IL-10), and C-reactive protein (CRP) were isolated and quantified. These biomarkers were detected using enzyme-linked immunosorbent assay (ELISA) and the corresponding kits. The analyses and results were conducted and provided by the clinical laboratory of our hospital.

2.3.6 Length of hospital stay and the primary outcome measures

Statistics and compare duration of mechanical ventilation between groups and the two groups' mortality within 28 days of hospitalization.

2.4 Statistical analysis methods

Data analysis was conducted using the Statistical Package Social Sciences (SPSS) Version 23.0 (IBM SPSS, Chicago, IL, USA) software after quantitative processing. Categorical data are presented as frequencies (percentages) and analyzed using the chi-square test. Continuous data, assessed for normal distribution conformity, are represented by the mean values and analyzed using the independent samples t-test. The Kaplan-Meier method was utilized to calculate the 28-day survival rates of the patients. A p-value of less than 0.05 was considered to denote a statistically significant difference.

3. Results

3.1 Baseline data comparison of the patients

Table 1 presents the baseline characteristics of patients in both groups. Comparisons of age, sex distribution, serological indices, APACHE II and SOFA scores revealed no significant differences between the two groups ($p > 0.05$).

TABLE 1. Baseline data of the investigated cohorts.

Variables	Placebo group (n = 50)	EPO group (n = 50)	t/χ^2	p
Age	58.53 ± 9.69	59.43 ± 10.91	0.435	0.665
Gender ratio (male/female)	37/13	34/16	0.437	0.509
WBC (10^9/L)	11.38 ± 2.98	11.64 ± 2.62	0.465	0.643
Neutral ratio	80.32 ± 11.53	79.80 ± 12.39	0.215	0.831
Platelet count (10^9/L)	169.56 ± 20.77	166.99 ± 22.38	0.593	0.554
Hemoglobin (g/L)	110.28 ± 14.91	111.27 ± 11.35	0.375	0.708
TBIL (μmol/L)	34.92 ± 4.91	35.49 ± 4.77	0.589	0.557
Albumin (g/L)	27.58 ± 3.58	26.26 ± 3.41	1.885	0.062
Cr (μmol/L)	121.84 ± 24.55	132.32 ± 38.44	1.624	0.108
Urea nitrogen (μmol/L)	11.64 ± 1.67	11.47 ± 1.92	0.480	0.633
PCT (μg/L)	3.12 ± 0.30	3.16 ± 0.40	0.455	0.650
APACHE II	18.09 ± 2.61	17.77 ± 2.21	0.656	0.514
SOFA score	6.81 ± 1.55	6.44 ± 1.60	1.195	0.235

EPO: Erythropoie; WBC: white blood cell; TBIL: total bilirubin; Cr: creatinine; PCT: procalcitonin; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sepsis-Related Organ Failure Assessment.

3.2 Comparison of heart rate and mean arterial pressure between groups

Heart rate and mean arterial pressure results of patients between the two groups before treatment and on days 7 and 14 of treatment are shown in Table 2. According to the table, the heart rate of patients in the same group decreased to different extents on the 7th and 14th day of treatment compared with that before treatment, while the heart rate of patients in the same group was similar at three different time points compared with that before treatment, and the differences were not statistically significant (t = 0.456, 1.065, 0.625, p = 0.649, 0.289, 0.534). Compared with that before treatment in the same group, the mean arterial pressure on the 7th and 14th day of treatment in the two groups showed various degrees of increase, but the mean arterial pressure level of the patients was similar at the same time period between the two groups, and the differences were not statistically significant (t = 0.341, 1.727, 0.449, p = 0.734, 0.087, 0.655).

3.3 Comparison of blood gas analysis indicators between groups

The results of blood gas analysis parameters of patients between groups are presented in Table 3. Before treatment, the PaO_2, $PaCO_2$ and oxygenation index were similar between the two groups, and the difference was not statistically significant (t = 0.397, 1.291, 0.395, p = 0.692, 0.200, 0.693). Compared with that before treatment in the same group, the PaO_2 and oxygenation index levels on days 7 and 14 of treatment showed different degrees of an increasing trend, while the $PaCO_2$ levels showed a decreasing trend compared with that before treatment. PaO_2 and oxygenation index levels on days 7 and 14 of treatment in the EPO group were significantly higher than those in the placebo group (t PaO_2 = 4.548, 6.762, t oxygenation index = 2.543, 2.547, $p < 0.05$), and the $PaCO_2$ levels on days 7 and 14 of treatment were markedly lower than those in the placebo group, and the differences were statistically significant (t = 2.860, 3.082, $p < 0.05$).

3.4 Comparison of function of lung volume between groups

The results of function parameters of lung volume between groups are shown in Table 4. Before treatment, the lung volume and FRC levels were similar between both groups, and the difference was not statistically significant (t = 1.764, 0.841, p = 0.081, 0.402). Lung volume and FRC levels were increased in the placebo and EPO groups on day 7 compared to before treatment, while lung volume and FRC levels were higher on day 14 of treatment than on day 7. In addition, the lung volume and FRC were significantly higher on days 7 and 14 compared to the placebo group (t day 7 = 6.966, 5.750, t day 14 = 4.928, 2.337, $p < 0.05$).

3.5 Comparison of inflammatory factor levels between groups

The results of inflammatory factor testing in patients between groups are shown in Table 5. Before treatment, the levels of TNF-α, IL-10 and CRP in both groups were similar, and the difference was not statistically significant (t = 0.808, 0.459, 0.143, p = 0.421, 0.649, 0.886). However, compared with that before treatment in the same group, the levels of TNF-α, IL-10 and CRP in the EPO group were significantly lower than that in the placebo group on the 7th and 14th day of treatment (t TNF-α = 5.750, 8.833, t IL-10 = 6.543, 12.049, t CRP = 4.782, 10.755, $p < 0.05$).

TABLE 2. Comparison of heart rate and mean arterial pressure between groups.

Groups	Testing time	Heart rate (beats/min)	Mean arterial pressure (mmHg)
Placebo group (n = 50)			
	Before treatment	124.14 ± 12.28	77.47 ± 7.30
	On day 7 of treatment	103.66 ± 8.94	85.20 ± 6.69
	On day 14 of treatment	93.89 ± 8.91	90.13 ± 6.84
EPO group (n = 50)			
	Before treatment	125.28 ± 12.62	77.94 ± 6.55
	On day 7 of treatment	101.64 ± 10.03	82.68 ± 7.82
	On day 14 of treatment	92.79 ± 8.83	87.11 ± 7.97

EPO: Erythropoie.

TABLE 3. Comparison of blood gas analysis indicators between groups.

Groups	Testing time	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	Oxygenation index
Placebo group (n = 50)				
	Before treatment	55.94 ± 5.37	49.74 ± 6.02	208.05 ± 40.49
	On day 7 of treatment	68.45 ± 7.97	45.77 ± 4.31	235.97 ± 43.43
	On day 14 of treatment	75.25 ± 6.37	42.61 ± 3.39	287.29 ± 60.34
EPO group (n = 50)				
	Before treatment	55.51 ± 5.55	51.39 ± 6.72	211.61 ± 49.15
	On day 7 of treatment	75.06 ± 6.49*	43.16 ± 4.83*	263.06 ± 61.51*
	On day 14 of treatment	84.23 ± 6.91*	40.41 ± 3.72*	321.83 ± 74.53*

*Note: *Table showed that there was a significant difference compared with the placebo group during the same period.*
PaO_2: partial pressure of oxygen; $PaCO_2$: partial pressure of carbon dioxide; EPO: Erythropoietin.

TABLE 4. Comparison of function of lung volume between the groups.

Group	Testing time	Lung volume (mL)	FRC (mL)
Placebo group (n = 50)			
	Before treatment	1543.59 ± 259.88	1059.63 ± 111.10
	On day 7 of treatment	2076.39 ± 263.14	1127.72 ± 239.54
	On day 14 of treatment	2280.95 ± 175.24	1621.71 ± 254.93
EPO group (n = 50)			
	Before treatment	1632.19 ± 242.17	1042.39 ± 93.06
	On day 7 of treatment	2404.42 ± 204.01	1359.31 ± 154.08
	On day 14 of treatment	2449.20 ± 166.06	1747.12 ± 281.00

FRC: functional residual capacity; EPO: Erythropoie.

TABLE 5. Comparison of inflammatory factor levels between groups.

Group	Testing time	TNF-α (pg/mL)	IL-10 (pg/mL)	CRP (mg/L)
Placebo group (n = 50)				
	Before treatment	42.00 ± 8.99	28.70 ± 4.30	33.33 ± 3.43
	On day 7 of treatment	29.75 ± 5.16	18.26 ± 3.35	19.03 ± 6.97
	On day 14 of treatment	22.22 ± 3.81	14.68 ± 2.06	12.97 ± 2.45
EPO group (n = 50)				
	Before treatment	40.54 ± 9.09	29.11 ± 4.70	33.21 ± 5.44
	On day 7 of treatment	23.73 ± 5.31*	14.67 ± 1.93*	13.45 ± 4.42*
	On day 14 of treatment	15.94 ± 3.27*	10.28 ± 1.56*	8.10 ± 2.06*

*Note: *Table showed that there was a significant difference compared with the placebo group during the same period. TNF: tumor necrosis factor; IL: interleukin; CRP: C-reactive protein; EPO: Erythropoietin.*

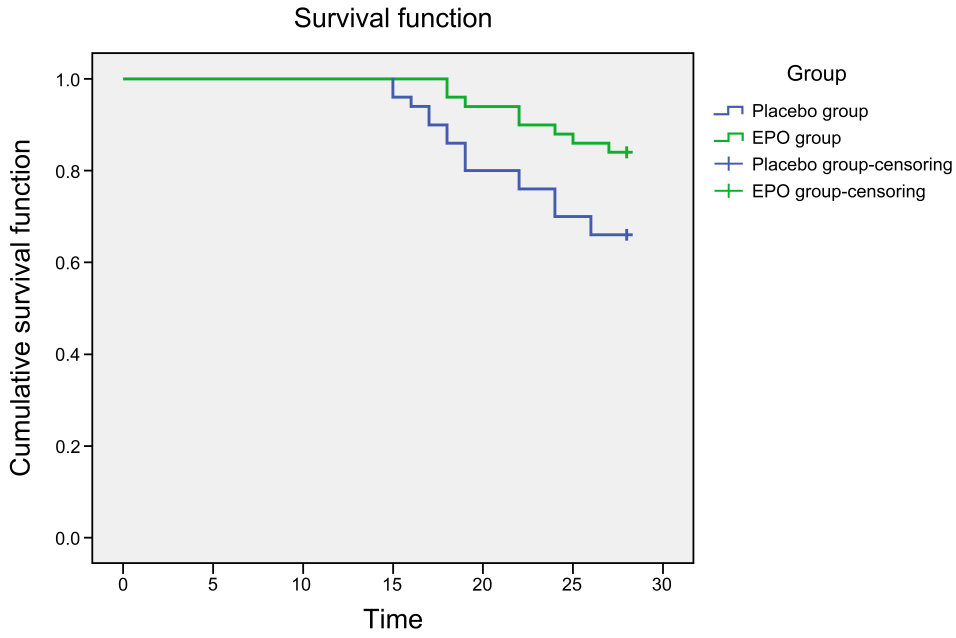

FIGURE 1. Survival curve within 28 days after hospitalization in the two groups. EPO: Erythropoietin.

3.6 Duration of mechanical ventilation and 28-day mortality

The mean duration of mechanical ventilation was 7.48 ± 1.80 days in the placebo group and significantly shorter in the EPO group at 5.47 ± 1.28 days (t = 6.434, $p < 0.05$). Within a 28-day hospitalization period, the EPO group experienced 8 deaths, resulting in a mortality rate of 16.00%, and an average survival time of 27.020 ± 0.364 days with a 95% confidence interval (CI) ranging from 26.307 to 27.733 days. Conversely, the placebo group had 17 deaths, translating to a mortality rate of 34.00%, and an average survival time of 25.300 ± 0.610 days, with a 95% CI between 24.104 and 26.469 days. A significant difference in survival rates between the two groups was identified (Log-Rank test, χ^2 = 4.651, p = 0.031), as demonstrated in Fig. 1.

4. Discussion

ARDS is a common critical illness in the intensive care unit (ICU). Available data suggest that over 10% of ICU admissions are due to ARDS, with a mortality rate ranging between 30% and 50% [12, 13]. Survivors often endure irreversible cerebral damage, leading to cognitive impairment, diminished lung capacity, and reduced exercise tolerance, significantly impacting their quality of life [14]. The association between sepsis and the progression of ARDS, particularly in critically ill patients, has been well-documented. The incidence of ARDS secondary to sepsis is higher, with mortality rates potentially reaching 70% to 90%, substantially exceeding those associated with non-septic ARDS [15]. The heterogeneity of ARDS contributes to variable patient responses to treatment. Currently, the management of septic ARDS lacks a swift and effective protocol, with strategies limited to pharmacotherapy, supportive care, and targeted interventions [16]. EPO, a 30.4 kDa endogenous glycoprotein hormone, is renowned for its role in erythropoiesis and enhancing oxygen delivery. Furthermore, EPO has been attributed with organoprotective properties in various contexts, including ischemia-reperfusion injury, neural damage, inflammation, and trauma across both animal studies and clinical trials [17–19]. Notably, EPO has shown the potential to reduce lung injury in pneumonia models by inhibiting neutrophil extracellular trap (NET) formation. This study employs normal saline as a placebo to contrast with EPO treatment, aiming to elucidate EPO's effects on septic ARDS, focusing particularly on alterations in blood gas parameters, lung volumes, and levels of inflammatory markers in patients.

Sepsis-associated ARDS often results in elevated capillary permeability, diminishing lung compliance, leading to decreased lung volume and subsequent hypoxemia; thus, enhancing respiratory mechanics and addressing the hypoxic condition are essential for lowering mortality in these patients [20]. The findings of this study indicated no significant differences in heart rate and mean arterial pressure between patients treated with EPO and those given the placebo, suggesting minimal impact of EPO on patient hemodynamics. However, blood gas analysis revealed improved PaO_2, $PaCO_2$ and oxygenation index levels in the EPO group compared to the placebo group on treatment days 7 and 14. EPO, an oxygen-regulated hormone, enhances erythropoiesis by activating hypoxia-inducible factors that stimulate the proliferation, differentiation, and maturation of erythroid progenitor cells in the bone marrow, thereby ameliorating the hypoxic state [21]. In addition, our results showed that the lung volume and FRC of patients in the EPO group were significantly increased compared with that in the placebo group, suggesting that the alveolar compliance of patients in the well-ventilated area was better, and combined with the improvement of compliance and oxygenation indicators, it can be observed that the pulmonary function of patients was better. Inflammatory factor infiltration is an important factor related to the progression of sepsis-induced diseases. The sepsis-mediated inflammatory cascade can lead

to alterations in the alveolar-capillary endothelial barrier's permeability, precipitating significant respiratory system damage. Thus, the administration of active anti-inflammatory and anticoagulant therapies is beneficial in the management of ARDS triggered by sepsis [22, 23]. Our study results demonstrated that the levels of TNF-α, IL-10 and CRP were significantly lower in the EPO group compared to the placebo group at both the 7th and 14th days of treatment, indicating that EPO effectively enhances the anti-inflammatory response, thereby diminishing neutrophil infiltration and the subsequent inflammatory injury caused by adhesion. These findings align with prior research indicating that EPO can reduce neutrophil infiltration into lung tissue [24, 25]. Nevertheless, the precise mechanism behind EPO's anti-inflammatory effects warrants further investigation. Additionally, we evaluated the average duration of mechanical ventilation and the mortality rate within 28 days of hospitalization among patients receiving either treatment regimen and observed that the EPO group had a significantly shorter duration of mechanical ventilation and a lower mortality rate compared to the placebo group, suggesting that this treatment regimen aids more effectively in disease recovery and decreases the short-term mortality associated with sepsis and ARDS, which could be related to EPO's role in ameliorating hypoxemia and diminishing the inflammatory response.

5. Conclusions

In this study, we explored the effects of EPO, and our findings demonstrate that EPO enhances the therapeutic outcomes in patients with sepsis-associated ARDS by improving blood gas metrics, augmenting lung volume functionality and attenuating serum levels of inflammatory mediators. As a multifunctional endogenous regulator, EPO could be a promising therapeutic agent for sepsis-induced ARDS. Nevertheless, concerns regarding the safety, optimal dosing and protective mechanisms of EPO remain to be addressed, urging the need for further comprehensive trials and clinical investigations.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

LJ and XX—designed the study and carried them out. LJ, XX, WXZ and JQC—supervised the data collection, analyzed the data, interpreted the data. LJ, XX, WXZ, JQC, JHY and WZ—prepared the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of Sir Run Run hospital of Nanjing Medical University (2022-SR-S037). Written informed consent was obtained from legally authorized representatives for anonymized patient information to be published in this article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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