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Original Article

Efficacy of Xuebijing injection in the adjunctive therapy of acute respiratory distress syndrome caused by sepsis

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Abstract: Objective: This study aimed to investigate the efficacy in the treatment of acute respiratory distress syndrome (ARDS) caused by sepsis and assisted by Xuebijing injection and its effect on serum inflammatory factors. Methods: Sixty-four patients with ARDS caused by sepsis were enrolled as observation subjects, and divided by random number table (n=32) into the control group treated with ulinastatin and the study group treated with ulinastatin assisted by Xuebijing injection. Patients in the two groups were compared in terms of blood gas indexes (partial pressure of oxygen (PaO_2), oxygenation index (PaO_2/FiO_2)), inflammatory factors (tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), interleukin-8 (IL-8), C-reactive protein (CRP), procalcitonin (PCT)), mean arterial pressure (MAP), heart rate (HR), invasive ventilation time, intensive care unit (ICU) monitoring time, length of stay (LOS), extravascular lung water index (ELWI) and acute physiology and chronic health evaluation scoring system (APACHE-II) scores. Results: The differences in PaO_2 and PaO_2/FiO_2 before and after treatment in the study group were significantly greater than those in the control group (both $P<0.05$). Meanwhile, the study group had the higher differences of TNF-α, IL-6, IL-8, PCT and CRP before and after treatment than the control group (all $P<0.05$). What's more, the differences in MAP, HR and ELWI in the study group were significantly greater than the control group (all $P<0.05$). The study group also showed a better improvement in APACHE II than the control group ($P<0.05$). Invasive ventilation time, ICU monitoring time and LOS were significantly shorter in the study group than in the control group (all $P<0.05$). Conclusion: In conclusion, the treatment of ARDS caused by sepsis assisted by Xuebijing injection can relieve the inflammatory response of patients with the disease, reduce the release of inflammatory factors and improve blood gas levels, HR and blood pressure, as well as promote the recovery and shorten invasive ventilation time, ICU monitoring time and LOS. Hence, it is worthy of popularization and application.

Keywords: Xuebijing injection, sepsis, acute respiratory distress syndrome, blood gas, inflammatory factor, ELWI

Introduction

Sepsis, a systemic inflammatory response syndrome caused by severe trauma, shock and infection, easily leads to multiple organ dysfunction syndrome (MODS). The lung is the first organ involved, so sepsis can cause diffuse alveolar damage and induce acute respiratory failure that is clinically manifested as acute respiratory distress syndrome (ARDS) [1, 2]. Due to its severity and rapid development, sepsis has a mortality of 20%-50% and is in urgent need of being effectively treated. In addition, inflammatory response and immune dysfunction are the main causes of death in these patients [3]. At present, ARDS secondary to sepsis is mainly treated by treating the infection, mechanical ventilation and other symptomatic support interventions in clinical practice [4]. However, the efficacy is unsatisfactory and the overall morbidity control is poor, with a high mortality. As a protease inhibitor extracted from human urine, ulinastatin significantly improves the immune function of patients with acute lung injury caused by sepsis, shortens the time of mechanical ventilation and LOS, and improves prognosis; as a result it is an important drug for the clinical treatment of acute lung injury caused by sepsis, according to a study [5].

Made from five traditional Chinese medicines, Safflower, Radix Paeoniae Rubra, Rhizoma Chuanxiong, Salvia Miltiorrhiza and Chinese Angelica, Xuebijing, via injection clears heat and detoxicates, promotes blood circulation

and removes blood stasis, dredges the channel and disperses toxins. Modern pharmacological studies show that in addition to resisting bacterial toxins and reducing endotoxin levels, it also regulates immunity, reduces inflammatory medium level and improves microcirculation, as well as protects vascular endothelial cells, and is a common treatment for sepsis [6, 7]. Related studies show that the clinical application of Xuebijing injection significantly alleviates the inflammatory response in patients with sepsis, improves coagulation function and accelerates the recovery of patients [8, 9]. However, there are few reports on the efficacy by comparison in the treatment of patients with ARDS caused by sepsis between ulinastatin alone and assisted by Xuebijing injection. Therefore, 64 patients with ARDS caused by sepsis were enrolled in this study in order to observe and compare the efficacy of Xuebijing injection and ulinastatin in patients with the disease. The report is as follows.

Materials and methods

General information

Sixty-four patients with ARDS caused by sepsis admitted to Linyi Central Hospital from June 2016 to June 2018 were enrolled as observation subjects. Inclusion criteria: (1) Patients met the diagnostic criteria for sepsis in the guidelines for the management of severe sepsis and septic shock in 20-12 and the diagnostic criteria for ARDS in the guidelines for the diagnosisandtreatmentofacu-telunginjury/acute respiratory distre-ss syndrome developed by the Socie-ty of Critical Care Medicine, Chinese Medical Association in 2006 [10, 11]; (2) patients older than or equal to 30 years old and younger than 60 years old; (3) patients and their families were informed and agreed. Exclusion criteria: (1) Patients complicated with autoimmune diseases; (2) patients complicated with severe cardiovascular and cerebrovascular diseases; (3) patients complicated with malignant tumors; (4) patients complicated with viral liver diseases; (5) patients allergic to drugs in this study; (6) pregnant and lactating women. This study was approved by the Medical Ethics Committee. Using the random number table, the patients were divided into the control group and the study group, with 32 patients in each group. There was no significant difference in comparison of general information, which means the two groups were comparable (**Table 1**).

Treatment methods

Patients in both groups were treated for anti-infection (Meropenem, Sumitomo Pharmaceuticals (Suzhou) Co., Ltd., China; 1 g, q8h, intravenous infusion), acid suppression and stomach protection (Omeprazole, Livzon Pharmaceutical Group Inc. Livzon Pharm, China; 40 mg, bid, intravenous infusion), and with mechanical ventilation, blood purification (Gambro AB, Beijing, China), correction of water and electrolytes. On the basis of these routine treatments, patients in the control group were intravenously infused with 200,000 U of ulinastatin (Techpool, Guangdong) + 50 mL of sodium chloride solution (at a concentration of 0.9%), every 4 h for 7 consecutive days of treatment. In addition to the treatment received by the control group, patients in the study group were also intravenously infused with 50 mL of Xuebijing injection (Tianjin Chase Sun Pharmaceutical Co., Ltd.) + 50 mL of sodium chloride solution (with a concentration of 0.9%), once every 12 h, for 7 consecutive days of treatment.

Outcome measures

Main outcome measures: (1) Blood gas analysis indexes: 0.5 mL of femoral arterial blood was collected from the patient before and 7 days after treatment, in order to detect PaO_2 and PaO_2/FiO_2 levels using an Abbott 300 blood gas analyzer from USA. (2) Inflammatory factor levels: The fasting elbow venous blood was extracted from the patient before and after treatment to detect TNF-α, IL-6, IL-8, CRP and PCT levels using ELISA (ELISA kit from Boster Biological Technology Co., Ltd., Wuhan, China; the microplate reader from Thermo, USA), with the operation carried out according to the reagent instructions. (3) An ECG monitor (model: 1500, Spacelab, USA) was used to detect changes in MAP and HR before and after treatment. (4) A PiCCO catheter (Pulsion, Germany) was inserted in the femoral artery and connected to the PiCCO detector, in order to detect changes in ELWI before and after treatment. (5) APACHE-II score was important for evaluating the condition and prognosis of critically ill patients as it was used for evaluating the disease severity and prognosis of the patients by quantitative rating [12]. It was mainly composed of acute physiology, age and chronic health sc-ores, with a final score of the sum of the three scores. The higher the score was, the more severe the condition was.

Table 1. Comparison of general information

Groups	Study group (n=32)	Control group (n=32)	χ^2/t	P
Gender			0.638	0.425
Male	23	20		
Female	9	12		
Age (year)	52.3±7.7	53.4±6.2	0.629	0.531
Shock			0.075	0.784
Have	10	9		
None	22	23		
Blood culture			0.277	0.599
G-	20	22		
G+	12	10		
Types of infection				
Postoperative gastrointestinal infection	12	15	0.577	0.448
Acute pancreatic infection	10	9	0.075	0.784
Pulmonary infection	10	8	0.309	0.578

Note: G-: Gram-negative bacterium; G+: Gram-positive bacteria.

Table 2. Comparison of blood gas indexes before and after treatment between the two groups ($\bar{x}$ ± sd)

Groups	Study group (n=32)	Control group (n=32)	t	P
PaO_2 (mmHg)				
Before treatment	61.48±6.62	62.76±5.94		
After treatment	90.31±4.25	82.85±4.37		
Difference before and after treatment	28.83±2.95	20.09±2.39	13.022	0.000
PaO_2/FiO_2				
Before treatment	129.41±18.43	128.83±19.24		
After treatment	202.04±15.32	81.68±13.29		
Difference before and after treatment	72.63±3.69	52.85±6.07	20.840	0.000

Note: PaO_2: partial pressure of oxygen; PaO_2/FiO_2: oxygenation index.

Secondary outcome measures were invasive ventilation time, ICU monitoring time and LOS. Invasive ventilation time was defined as the time from the beginning of invasive ventilation to weaning from mechanical ventilation. LOS was defined as the time from the diagnosis of ARDS caused by sepsis to discharge. ICU monitoring time was defined as the time from stay in the ICU to transfer out of the ICU.

Statistical analysis

SPSS 19.0 statistical software was used for analysis. Measurement data are expressed by mean ± standard deviation ($\bar{x}$ ± sd). Independent t test was used for comparison between groups, and paired t test was used for the comparison of the value itself before and after treatment. Count data are expressed by the number of cases/percentage (n/%), and the χ^2 test was used for comparison. When P is less than 0.05, the difference is statistically significant.

Results

Improvement of blood gas analysis after treatment of Xuebijing injection combined with ulinastatin

Before treatment, PaO_2 and PaO_2/FiO_2 were not significantly different between the two groups of patients (all P>0.05), but were significantly increased after treatment. The differences in PaO_2 and PaO_2/FiO_2 before and after treatment were significantly greater in the study group than those in the control group (both P<0.05). This indicated that Xuebijing injection com-

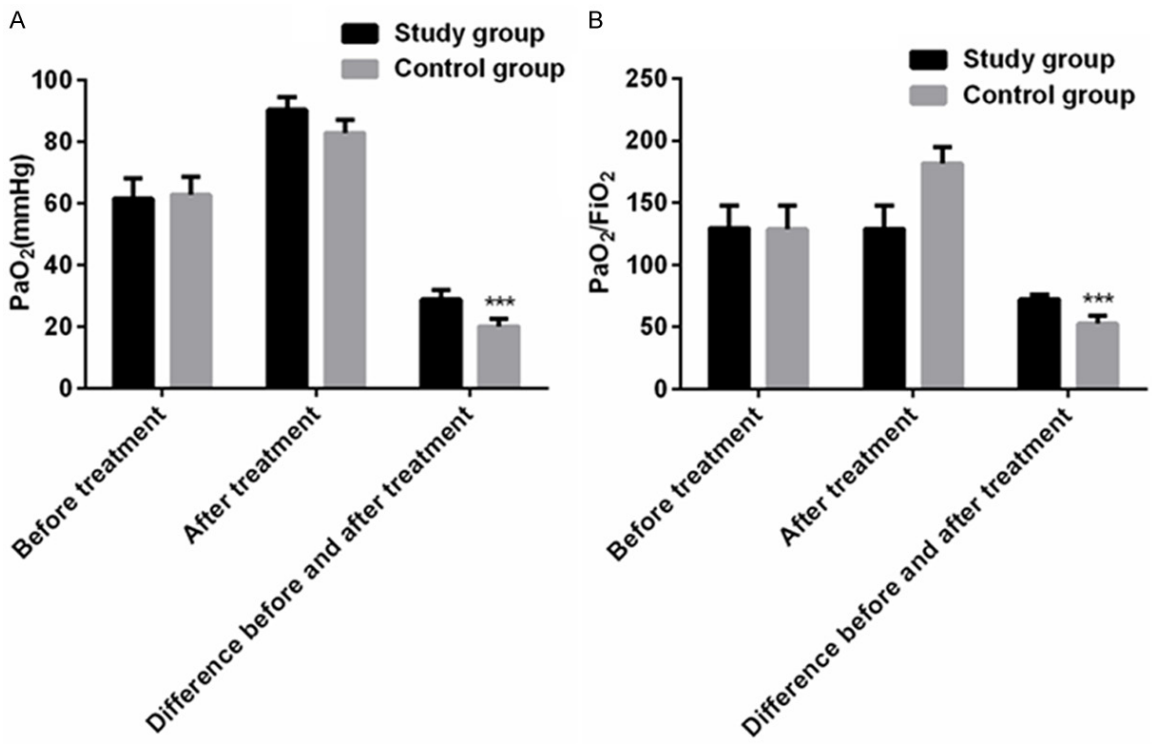

Figure 1. Comparison of blood gas indexes before and after treatment between the two groups. A: Comparison of PaO_2 before and after treatment between the two groups. B: Comparison of PaO_2/FiO_2 before and after treatment between the two groups. Compared with the study group, ***P<0.001. PaO_2: partial pressure of oxygen; PaO_2/FiO_2: oxygenation index.

Table 3. Comparison of inflammatory factors before and after treatment between the two groups ($\overline{x}$ ± sd)

Groups	TNF-α (ng/L)	IL-6 (ng/L)	IL-8 (ng/L)	PCT (μg/L)	CRP (mg/L)
Study group (n=32)					
Before treatment	143.72±26.25	76.94±8.27	64.08±22.29	6.73±3.06	78.42±9.78
After treatment	89.23±20.56	27.34±6.58	27.82±11.74	0.96±0.28	29.15±3.07
Control group (n=32)					
Before treatment	143.21±24.93	76.38±7.95	63.76±24.37	6.35±2.98	79.82±9.05
After treatment	122.25±23.08	59.42±9.17	52.35±15.49	2.14±1.44	47.86±4.21
Difference before and after treatment					
In study group	54.49±6.73	49.6±2.09	36.26±10.55	5.77±2.84	49.27±6.79
In control group	20.96±2.33	16.96±1.37	11.41±8.97	4.21±1.69	31.96±4.99
t	26.632	73.885	10.151	2.670	11.621
P	0.000	0.000	0.000	0.010	0.000

Note: TNF-α: tumor necrosis factor α; IL-6: interleukin-6; IL-8: interleukin-8; PCT: procalcitonin; CRP: C-reactive protein.

bined with ulinastatin can significantly improve the level of blood gas, with better efficacy than ulinastatin alone. See **Table 2** and **Figure 1**.

Reduction of inflammatory factors after Xuebijing injection combined with ulinastatin

Before treatment, TNF-α, IL-6, IL-8, PCT and CRP were not significantly different between the two groups (all P>0.05), and were decreased after treatment. The differences in those inflammatory factors before and after treatment were significantly greater in the study group than those in the control group (all P<0.05), which suggests a more remarkable improvement and better curative effect of Xuebijing injection combined with ulinastatin than ulinastatin alone. See **Table 3** and **Figure 2**.

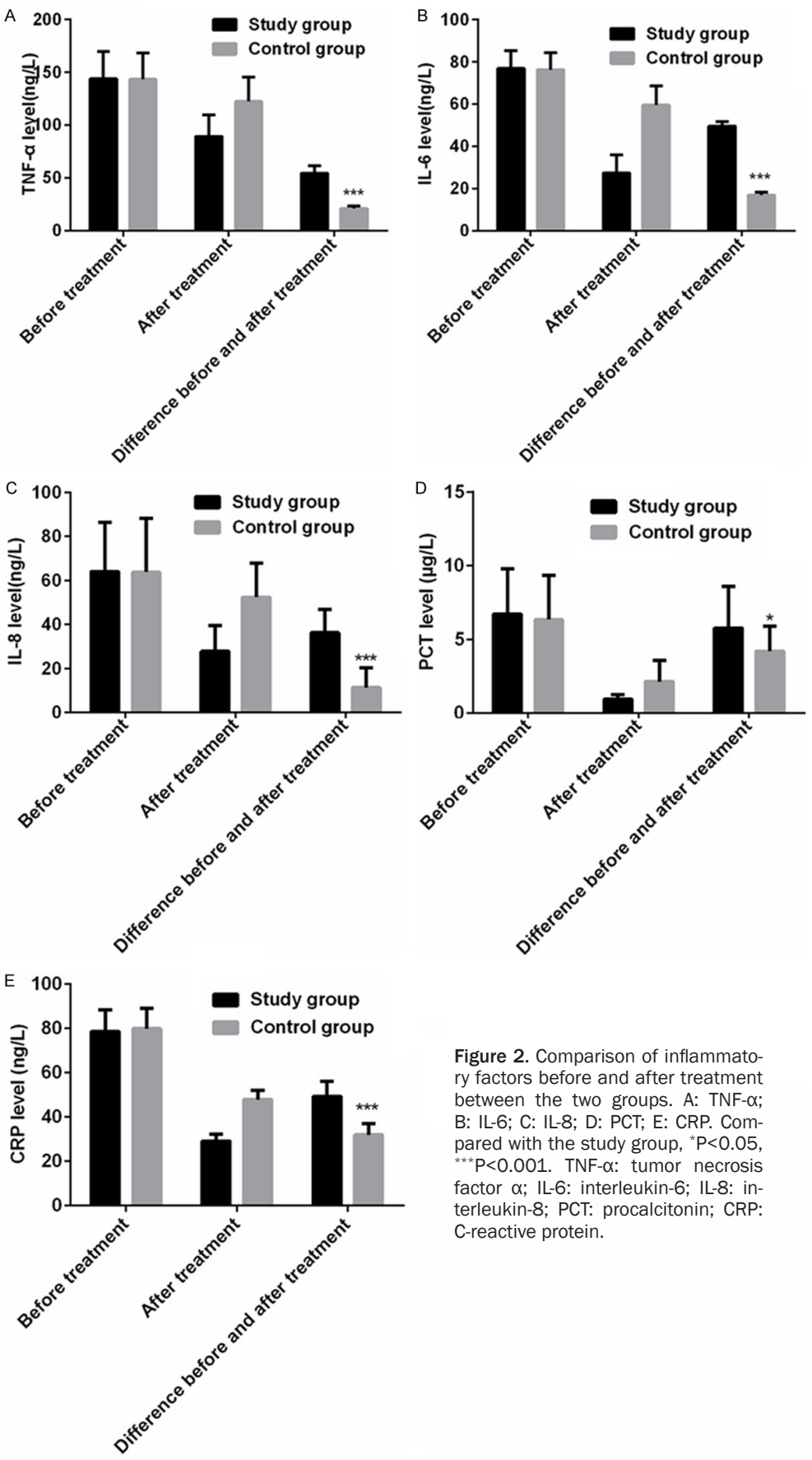

Figure 2. Comparison of inflammatory factors before and after treatment between the two groups. A: TNF-α; B: IL-6; C: IL-8; D: PCT; E: CRP. Compared with the study group, *P<0.05, ***P<0.001. TNF-α: tumor necrosis factor α; IL-6: interleukin-6; IL-8: interleukin-8; PCT: procalcitonin; CRP: C-reactive protein.

Table 4. Comparison of MAP, HR and ELWI before and after treatment between the two groups ($\bar{x} \pm sd$)

Groups	MAP (mmHg)	HR (time/min)	ELWI (mL/kg)
Study group (n=32)			
Before treatment	74.65±3.13	122.87±5.43	14.94±1.62
After treatment	84.63±3.22	96.48±3.81	8.89±0.97
Control group (n=32)			
Before treatment	73.98±2.94	123.15±5.29	14.56±1.78
After treatment	79.25±3.07	102.29±3.64	10.86±1.02
Difference before and after treatment			
In study group	9.98±1.24	26.39±1.87	6.05±0.95
In control group	5.27±0.95	20.86±1.65	3.73±0.85
t	17.057	12.544	10.295
P	0.000	0.000	0.000

Note: MAP: mean arterial pressure; HR: heart rate; ELWI: extravascular lung water index.

Stabilization of hemodynamic levels in patients with the treatment of Xuebijing injection combined with ulinastatin

Before treatment, MAP, HR and ELWI were not significantly different between the two groups (all P>0.05); after treatment, MAP was significantly higher, whereas HR and ELWI were decreased. The differences among the three indexes before and after treatment were significantly greater in the study group than those in the control group (all P<0.05). See **Table 4** and **Figure 3**.

Lowering of APACHE-II score after Xuebijing injection combined with ulinastatin

Before treatment, APACHE-II score was not significantly different between the two groups (both P>0.05), but was decreased after treatment. The study group showed greater differences of APACHE-II score before and after treatment than the control group (P<0.05), which demonstrates Xuebijing injection combined with ulinastatin can do better in disease relief. See **Table 5** and **Figure 4**.

Shortened invasive ventilation time, ICU monitoring time and LOS with the help of Xuebijing injection combined with ulinastatin

Invasive ventilation time, ICU monitoring time and LOS were significantly shorter in the study group than those in the control group (all P<0.05). It can be seen that Xuebijing injection combined with ulinastatin played a significant role in rehabilitation of patients. See **Table 6** and **Figure 5**.

Discussion

Sepsis causes alveolar capillary membrane damage, diffuse alveolar collapse, dyspnea, decrease in lung compliance and hypoxia in patients with ARDS, which easily leads to organ dysfunction and even death. Patients with ARDS caused by sepsis have a high inflammatory response and hypercoagulable status, and then inflammation and coagulation activate each other, which leads to a cascade effect and aggravates the patients' condition. ARDS caused by sepsis is routinely treated by anti-infection medication, mechanical ventilation and blood volume supplementation, with limited efficacy. Due to dyspnea and high inflammatory response in patients with the disease, how to effectively reduce inflammatory factors, relieve inflammatory response and improve blood gas during treatment has become the focus of clinical research.

In containing Radix Paeoniae Rubra, Chinese Angelica, Safflower, Salvia Miltiorrhiza and Rhizoma Chuanxiong, Xuebijing injection inhibits the release of inflammatory medium and increases fibrinogen, thereby inhibiting the inflammatory response, increases blood flow volume and strengthens the effect of tissue oxygen supply. Additionally, it promotes microcirculation and increases tissue blood flow, which thereby effectively reduces the pathological damage to the lung tissue under synthetic action. Ligustrazine in Rhizoma Chuanxiong, has a similar action as a calcium ion antagonist, which can inhibit calcium influx, enlarge blood vessels and improve tissue hypoxia. A study has shown that Xuebijing injection in the treatment of patients with severe sepsis in the ICU significantly reduces the elevated serum pro-inflammatory factor levels, improves clinical symptoms and protects organ

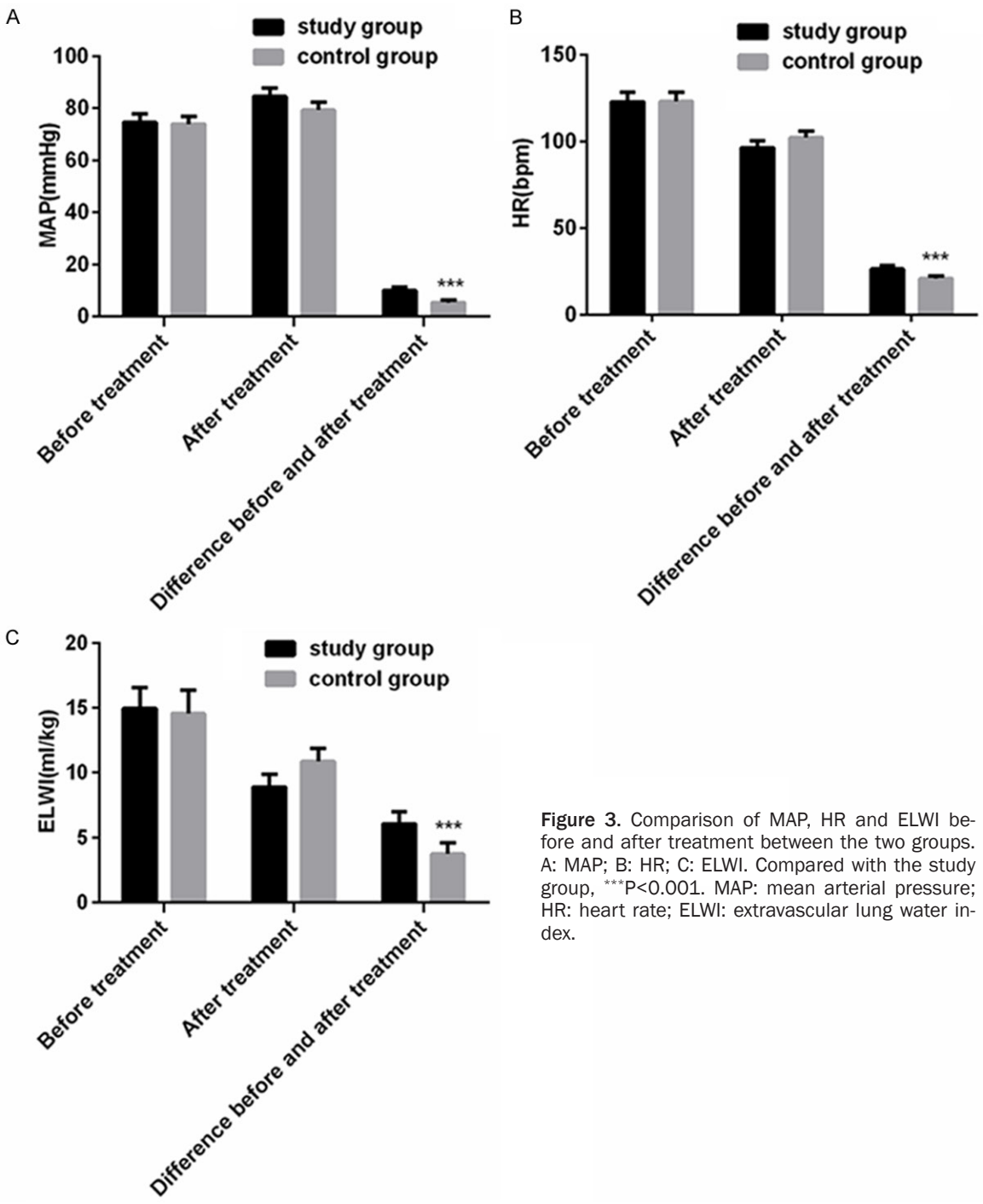

Figure 3. Comparison of MAP, HR and ELWI before and after treatment between the two groups. A: MAP; B: HR; C: ELWI. Compared with the study group, ***P<0.001. MAP: mean arterial pressure; HR: heart rate; ELWI: extravascular lung water index.

function, as well as improves the prognosis and reduces the 28-day fatality rate [13]. There is also a study reporting that Xuebijing injection improves lung injury caused by sepsis by down-reg-ulating HMGB1 and RAGE expression in mice, indicating that Xuebijing injection can improve lung injury caused by sepsis, in addition to treating sepsis [14]. The results of this study showed that compared with the control group, the study group had significantly greater differences in PaO_2, PaO_2/FiO_2 and MAP, significantly lower HR and APACHE-II scores, and significantly shorter invasive ventilation time, ICU monitoring time and LOS. The results suggest that Xuebijing injection can significantly improve hypoxia in patients with ARDS caused by sep-

Table 5. Comparison of APACHE-II score before and after treatment between the two groups ($\bar{x}$ ± sd)

Groups	Study group (n=32)	Control group (n=32)	t	P
APACHE-II score				
Before treatment	25.06±2.37	25.48±2.41		
After treatment	13.17±1.25	16.39±1.32		
Difference before and after treatment	11.89±1.68	9.09±1.44	7.158	0.000

Note: APACHE-II: acute physiology and chronic health evaluation scoring system.

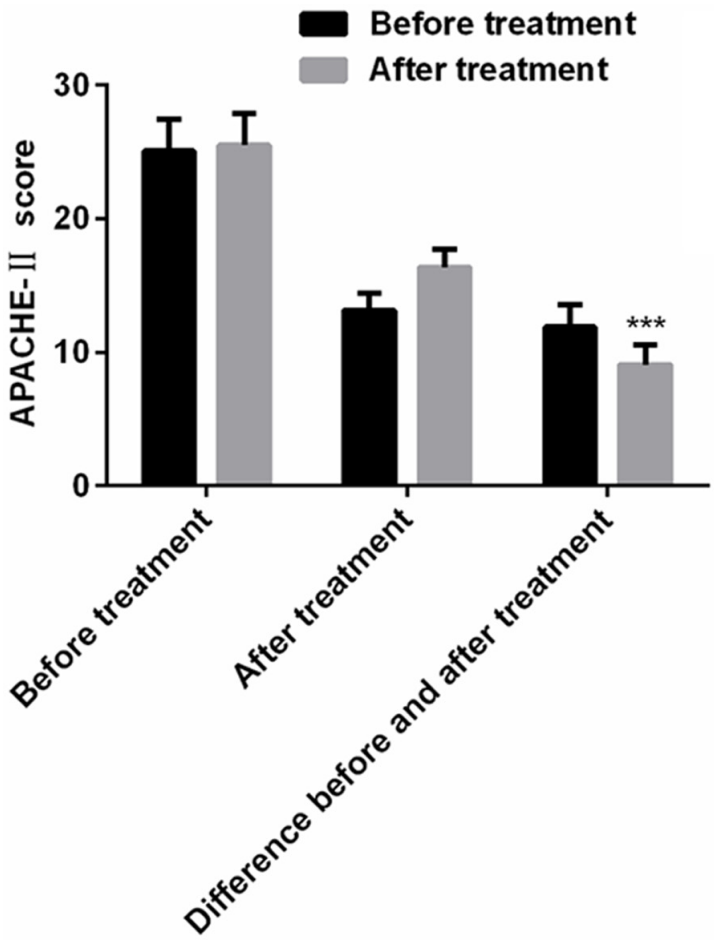

Figure 4. Comparison of APACHE-II score before and after treatment between the two groups. Compared with the study group, ***P<0.001; compared with the study group. APACHE-II: acute physiology and chronic health evaluation scoring system.

Table 6. Comparison of invasive ventilation time, ICU monitoring time and LOS between the two groups ($\bar{x}$ ± sd)

Groups	Study group (n=32)	Control group (n=32)	t	P
Invasive ventilation time	2.73±1.27	4.89±1.54	6.121	0.000
ICU monitoring time	6.71±1.48	15.32±4.56	10.159	0.000
LOS	17.74±2.83	26.82±4.97	8.981	0.000

Note: ICU: intensive care unit; LOS: length of stay.

sis, protect lung function and stabilize patients' vital signs, as well as shorten LOS, which is consistent with the reports in the literature [13].

TNF-α, IL-6, IL-8, PCT and CRP are clinically important indicators for diagnosing ARDS caused by sepsis and judging prognosis of the patients [15, 16]. CRP is a sensitive indicator for systemic acute inflammatory response, the increase in which usually indicates a systemic inflammatory response in the body [17]. PCT is a propeptide substance of calcitonin and an important indicator for the clinical diagnosis of inflammatory diseases and for early warning [18]. In the study by Huang et al., plasma PCT and CRP levels in patients with severe sepsis and ARDS are significantly in-creased, as they are significantly decrea-sed after the patients are treated by ulinastatin, indicates that PCT and CRP can reflect the severity of the disease in patients [19]. The results of this study showed that after treatment, CRP and PCT levels in the study group were significantly lower than those in the control group, suggesting that the adjuvant treatment with Xuebijing injection can significantly reduce CRP and PCT levels in patients with sepsis and ARDS, and alleviate the inflammatory response of the body, with better efficacy than the control group.

In patients with sepsis, TNF-α, IL-6 and IL-8 can be activated and released in large quantities, and stimulate the production of hydrolase and oxygen free radicals, which causes damage to the tissues and organs. Therefore, reducing the release of TNF-α, IL-6 and IL-8 helps protect the tissues and organs. In the study by Sun et al., TNF-α, IL-1 and IL-8 in the serum of

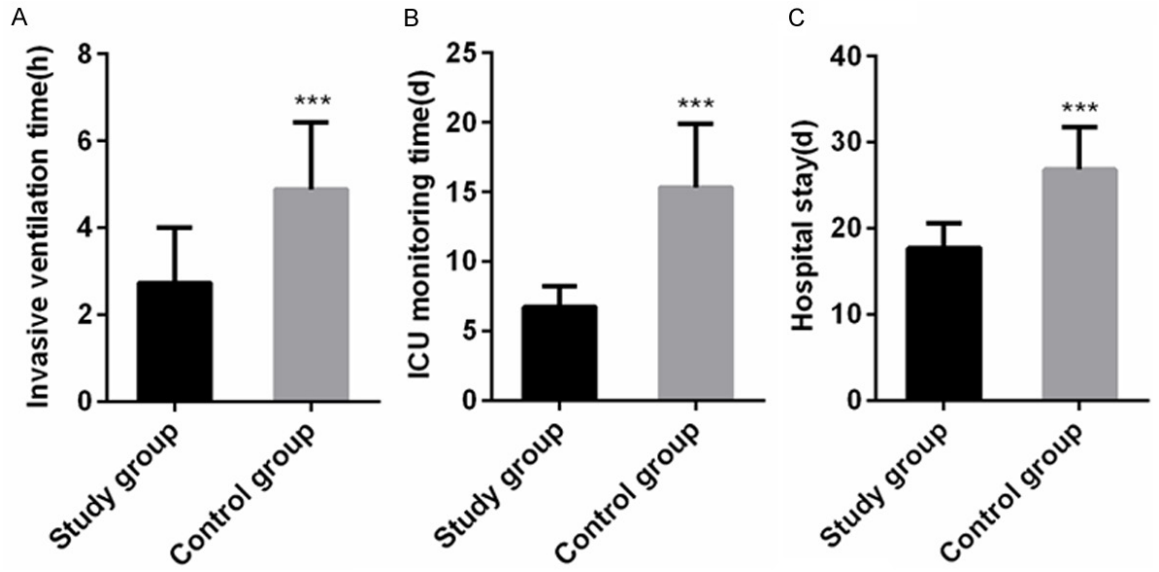

Figure 5. Comparison of invasive ventilation time, ICU monitoring time and LOS between the two groups. A: Invasive ventilation time. B: ICU monitoring time. C: LOS. Compared with the study group, ***P<0.001. ICU: intensive care unit; LOS: length of stay.

septic rats are significantly increased, indicating that inflammatory factors are excessively secreted by inflammatory stimulation, and their expression levels are significantly reduced after Xuebijing injection, indicating that Xuebijing injection significantly inhibits the excessive secretion of inflammatory factors caused by inflammatory stimulation [20]. This study showed that inflammatory factor indexes and blood gas indexes were significantly improved after the treatment of ARDS caused by sepsis assisted by Xuebijing injection, with better efficacy than the control group. The results are consistent with the report in the literature [21]. This study speculates that it may be related to the fact that safflower, red peony root and Danshen can improve capillary permeability, effectively reducing the in-flammatory exudation of the tissue and the release of inflammatory factors, and accelerate the absorption of the inflammation, as well as inhibit the inflammatory response.

However, this study only initially explored the preliminary efficacy of Xuebijing injection in patients with ARDS caused by sepsis. Due to the short study time, the long-term efficacy was not observed, and the specific pathways to improve the inflammatory state of patients with ARDS were not investigated. The observation time in the next study will be extended, the long-term efficacy will be explored, and animal experiments will be increased, in order to study the specific mechanisms of action.

In summary, the treatment of ARDS caused by sepsis assisted by Xuebijing injection can relieve the inflammatory reaction of patients with the disease, reduce the release of inflammatory factors and improve blood gas levels, HR and blood pressure, as well as promote the recovery and shorten invasive ventilation time, ICU monitoring time and LOS, so it is worthy of popularization and application.

Disclosure of conflict of interest

None.

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