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Clinical effect of Xuebijing combined with thymosin α1 on patients with severe pneumonia complicated with sepsis and its effect on serum inflammatory factors

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ABSTRACT

This study aimed to research the clinical effect of Xuebijing combined with thymosin α1 on patients with severe pneumonia complicated with sepsis, and its effect on serum inflammatory factors. For this purpose, 81 cases of severe pneumonia complicated with sepsis were collected. All patients were given early treatments. 41 cases who received Xuebijing injection by intravenous drip were selected as the control group. 40 cases who were treated through subcutaneous injection of thymosin α1 based on Xuebijing injection by intravenous drip were selected as the study group. The body temperature, respiration, heart rate, leukocytes, other general conditions, blood gas indexes, serum IL-6, TNF-α and CRP levels, bacterial clearance rate and therapy effect were recorded and compared before and after treatment. Results showed that after treatment, the body temperature, respiration, heart rate, leukocytes and other general conditions of the study group were lower than those in the control group (all $p<0.05$). The blood gas indexes pH and PaCO2 levels of the study group were lower than those of the control group. The levels of serum interleukin-6 (IL-6), serum tumor necrosis factor α (TNF-α) and C-reactive protein (CRP) in the study group were lower than those in the control group (all $p<0.05$). The bacterial clearance rate of the study group was lower than that of the control group (all $p<0.05$). The total effective rate of treatment of patients in the study group was higher than that of patients in the control group (all $p<0.05$). In general, Thymosin α1 and Xuebijing injection can improve the therapy effect of severe pneumonia complicated with sepsis, improve the hemorheology condition of patients, effectively remove bacteria and reduce the expression level of serum CRP, TNF-α, IL-6, IL-8 and other inflammatory factors in patients, which is worthy of clinical promotion.

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Introduction

Sepsis is a series of symptoms when an infection causes systemic inflammatory responses, including fever, leukocytosis or leukopenia, decreased vascular resistance, often leading to hypotension (sepsis shock), organ failure (severe sepsis) and death (1). The mortality rate of sepsis is about 20-30% (2). The incidence rate of sepsis is relatively high in the elderly. With the increase of the population age, the incidence of sepsis may significantly increase (3). In developed countries, the incidence of sepsis reaches 100/100,000 (4). Sepsis is a serious systemic infection response, and pneumonia is the main cause of sepsis (5). Sepsis begins with the epitope transfer of antigen-presenting cells to neutrophils, macrophages, and T helper lymphocytes (Th), followed by activation of the cellular transcription factor NF-KB, then enter into the nucleus and form the complexes with DNA. Subsequently, it induces apoptosis and activates Th lymphocytes into Thl cells, releasing a large number of pro-inflammatory cytokines and chemokines, such as TNF-α, IL-6 (6). Studies have also shown that CRP can be used as a marker for sepsis (7).

Xuebijing injection is a complex traditional Chinese herbal compound, which has been widely used in the treatment of sepsis in China (8). Pharmacological studies have shown that Xuebijing can block the progression of sepsis through antibacterial, anti-inflammatory, antiendotoxin and other ways, and is an effective drug to improve

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survival rate (9). Studies have also shown that Xuebijing injection combined with standardized treatment can reduce the mortality of patients with severe pneumonia, reminding that Xuebijing may be a potential and promising assistant treatment for severe pneumonia (10). Thymosin α1 is a peptide hormone whose immunomodulatory properties have been demonstrated *in vitro* and *in vivo* and approved for the treatment of several viral infections and cancers in different countries (11). Pharmacological studies have shown that thymosin α1 stimulates the secretion of endogenous IFN-γ, enhances T cells and the entire immune system (12). In the study of Chen et al (13), Xuebijing combined with ulinastatin was more effective in treating sepsis than ulinastatin alone. We speculate that the combination of Xuebijing and thymosin α1 could relieve the symptom with good efficacy in the treatment of severe pneumonia combined with sepsis.

Therefore, this study aims to provide a reference for the clinical treatment of severe pneumonia complicated with sepsis by exploring the clinical effect of Xuebijing combined with thymosin α1.

Materials and methods

Baseline data

81 cases of severe pneumonia complicated with sepsis who were admitted to our hospital from January 2013 to July 2016 were collected. Patients were divided into two groups according to different treatments. 41 cases who received Xuebijing injection by intravenous drip were selected as the control group. Among them, there were 25 males and 16 females. The age was 50-70 years old and the average age was (63.56±5.44) years old. 40 cases who were treated through subcutaneous injection of thymosin α1 on the basis of Xuebijing injection by intravenous drip were selected as study group. There were 26 males and 14 females. The age was 52-70 years and the average age was (64.33±5.32) years old. This study was approved by our hospital ethics committees. All patients have signed the informed consent.

Inclusion and exclusion criteria

Inclusion criteria: all patients met the therapeutic guide and diagnosis of Chinese adults' community-acquired pneumonia (14). All patients met the international guidelines on sepsis and sepsis shock management in 2016 (15) and had complete case data. All patients agree to cooperate with the medical staff of our hospital, and the informed consent forms were signed by the patients or their immediate relatives.

Exclusion criteria: patients who were applied with immunosuppressants in the last 3 months; patients with severe renal dysfunction and malignant tumor; patients with mental illnesses, language dysfunctions and diseases that affect the results of this study.

Methods

In both groups, 3 ml of peripheral venous blood was extracted on an empty stomach in the early morning in the hospital, and the serum was centrifuged for 12 min at a centrifuge radius of 15 cm, 3000 r/min, and then separated and stored at -80 ℃ for measurement. The pH and PaCO2 levels of patients were analyzed by ABL80 series blood gas analyzers produced by lei dumite medical equipment (Shanghai) co., LTD. The serum IL-6, TNF-α and IL-6 were detected by ELISA and detection kit was purchased from ultest biological technology co., LTD., Shanghai. The item number is (CS-13629E). The TNF-α test kit was purchased from Shanghai Jingsheng Bioengineering Co., Ltd., and the item number is (JK-(a)-2161). The C-reactive protein test kit was purchased from Shanghai Jingsheng Bio-engineering Co., Ltd., and the item number is (JKSJ--1376). The operation steps are strictly in accordance with the requirements of the manual.

Patients were given antibiotics to fight infection, regulate blood pressure and blood sugar, correct acid-base balance, respiratory and nutritional support and other routine treatments. The control group was injected with Xuebijing (purchased from Tianjin Chase Sun Pharmaceutical Co., Ltd., national drug approval number: Z20040033) on the basis of conventional treatment, 50 mg/time, adding 0.9% normal saline 100 ml intravenous drip for 30-40 min, 3 times/day, continuous treatment for 10 d. The research group was injected with thymosin α1 (purchased from chengdu diao jiuhong pharmaceutical co., LTD., national drug approval number: H20020545) in the base of Xuebijing by intravenous drip, 1.6 mg/ time, 1 time/day, continuous injection for 10 d.

Observation indices

Body temperature, respiration, heart rate, leukocytes, blood gas indexes, serum interleukin-6 (IL-6), serum tumor necrosis factor-α(TNF-α), C reactive protein (CRP) levels, bacterial clearance rate and efficacy of patients in the two groups.

Efficacy of criterion standard

Cure: breathing, body temperature, heart rate and leukocytes returned to normal. Marked effect: the condition improved significantly, but one of breathing, body temperature, heart rate and leukocytes did not return to normal. Effective: the condition improved, but the recovery of respiratory, temperature, heart rate and leukocytes was not obvious. Ineffective: the condition was unchanged or aggravated. Bacteriological efficacy was assessed on bacterial culture specimens, including clearance, hypothetical clearance, replacement, no clearance, and reinfection. Clinical effective rate = (number of cure cases + number of marked effect Cases + number of effective cases) / number of total cases in the group × 100%. Bacterial clearance rate = (number of clearance cases + number of hypothetical clearance cases + number of replacement cases) / total number of cases × 100%.

Statistical methods

All the experimental results were statistically calculated using SPSS24.0 statistical (Beijing Sitron Weida Information Technology Co., Ltd.), and the image was drawn using GraphPad Prism 7. Counting data was expressed as a percentage (%). The chi-square test was used to compare the two groups. All measurement data was expressed in the form of (mean number ± standard deviation). T-test was used for comparison between groups. The difference was statistically significant with $p<0.05$.

Results and discussion

Baseline data of patients

There were no significant differences in gender, age, BMI, place of residence, nation, smoking history, drinking history, marital status, family history and other baseline data ($p>0.05$) between the two groups. More details are shown in Table 1.

Table 1. Comparison of the baseline data of patients between the two groups

	Study group (40)	Control group (41)	t or F	*p*
Gender			0.141	0.709
Male	26 (65.00)	25 (60.98)		
Female	14 (35.00)	16 (39.02)		
Age/years old	64.33±5.32	63.56±5.44	0.644	0.522
BMI (kg/cm2)	22.47±2.83	22.15±2.62	0.528	0.599
Place of residence			0.004	0.953
City	31 (77.50)	32 (78.05)		
Rural	9 (22.50)	9 (21.95)		
Nation			0.863	0.353
Han nationality	36 (90.00)	34 (82.93)		
Minority nationality	4 (10.00)	7 (17.07)		
Smoking history			0.102	0.749
Yes	29 (72.50)	31 (75.61)		
No	11 (27.50)	10 (24.39)		
Drinking history			0.106	0.745
Yes	21 (52.50)	23 (56.10)		
No	19 (47.50)	18 (43.90)		
Marital status			0.240	0.624
Married	37 (92.50)	39 (95.12)		
Unmarried	3 (7.50)	2 (4.88)		
Family history			0.103	0.748
Yes	18 (45.00)	17 (41.46)		
No	22 (55.00)	24 (58.54)		

Comparison of general conditions such as body temperature, respiration, heart rate, leukocytes before and after treatment in the two groups

Temperature, respiration, heart rate, leukocytes and other general conditions before treatment were observed. In the study group, body temperature was (38.02±1.03) °C, respiration was (27.13±3.21) times /min, heart rate was (27.13±3.21) times /min and leukocytes was (17.13±7.43) ×109/L. In the control group, body temperature was (38.09±1.05) °C, respiration was (26.94±3.33) times /min, heart rate was (105.04±16.81) times /min and leukocytes was (16.97±7.29) ×109/L. There was no significant difference between the two groups (all $p>0.05$). After treatment, in the study group, body temperature was (37.10±0.51) °C, respiration was (20.75±1.82) times /min, heart rate was (75.86±11.69) times /min and leukocytes was (6.97±2.31) ×109/L. In the control group, body temperature was (37.52±0.59) °C, respiration was (23.65±2.03) times /min, heart rate was (81.94±12.43) times /min and leukocytes was (10.54±3.64) ×109/L. After treatment, body temperature, respiration, heart rate, leukocytes and other general conditions in the two groups were lower than those before treatment (all $p<0.05$). Body temperature, respiration, heart rate, leukocytes and other general conditions in the study group were lower than those in the control group (all $p<0.05$). More

details are shown in Figure 1. The description of each part of Figure 1 is as follows:

A: Comparison of body temperature before and after treatment in two groups of patients: after treatment, the body temperature of the control group was higher than that in the study group. The difference was statistically significant（all $p<0.05$). a represents the comparison before and after treatment in the control group ($^{a}p<0.05$). b represents the comparison before and after treatment in the study group ($^{b}p<0.05$). c represents the comparison between the control group and the study group after treatment ($^{c}p<0.05$).

B: Comparison of respiratory frequency before and after treatment in two groups of patients: after treatment, the respiratory frequency of the control group was higher than that in the study group. The difference was statistically significant（all $p<0.05$). a represents the comparison before and after treatment in the control group ($^{a}p<0.05$). b represents the comparison before and after treatment in the study group ($^{b}p<0.05$). c represents the comparison between the control group and the study group after treatment ($^{c}p<0.05$).

C: Comparison of heart rate before and after treatment in two groups of patients: after treatment, the heart rate of the control group was higher than that in the study group. The difference was statistically significant（all $p<0.05$). a represents the comparison before and after treatment in the control group ($^{a}p<0.05$). b represents the comparison before and after treatment in the study group ($^{b}p<0.05$). c represents the comparison between the control group and the study group after treatment ($^{c}p<0.05$).

D: Comparison of leukocytes before and after treatment in two groups of patients: after treatment, the leukocytes of the control group was higher than that in the study group. The difference was statistically significant（all $p<0.05$). a represents the comparison before and after treatment in the control group ($^{a}p<0.05$). b represents the comparison before and after treatment in the study group ($^{b}p<0.05$). c represents the comparison between the control group and the study group after treatment ($^{c}p<0.05$).

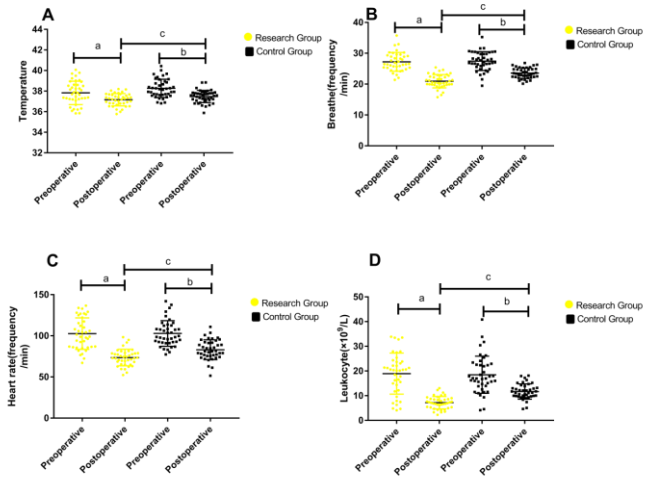

Figure 1. Comparison of general conditions such as body temperature, respiration, heart rate, leukocytes before and after treatment in the two groups. The description is given in the text.

Comparison of blood gas indexes before and after treatment in two groups of patients

Blood gas indexes before and after treatments were observed. Before treatment, the pH of the study group was (7.87±0.08), and the PaCO2 was (54.29±5.24) mmHG. In the control group, pH was (7.88±0.07) and PaCO2 was (53.98±5.21) mmHG. There was no significant difference between the two groups (all $p>0.05$). After treatment, the pH of the study group was (7.05±0.05) and PaCO2 was (35.18±5.29) mmHG. In the control group, pH was (7.31±0.07) and PaCO2 was (39.23±5.33) mmHG. After treatment, blood gas pH and PaCO2 levels of the two groups were lower than those before treatment (all $p<0.05$). The blood gas index pH and PaCO2 levels in the study group were lower than those in the control group (all $p<0.05$). More details are shown in Figure 2. The description of each part of Figure 2 is as follows:

A: Comparison of ph levels before and after treatment in two groups of patients: after treatment, the blood gas indexs ph levels of the study group was lower than that in the control group (all p<0.05). a represents the comparison before and after treatment in the control group ($^{a}p<0.05$). b represents the comparison before and after treatment in the study group ($^{b}p<0.05$). c represents the comparison between the control group and the study group after treatment ($^{c}p<0.05$).

B: Comparison of $PaCO_2$ levels before and after treatment in two groups of patients: after treatment, the $PaCO_2$ levels of the study group were lower than that in the control group (all p<0.05). a represents the comparison before and after treatment in the control group (^{a}p<0.05). b represents the comparison before and after treatment in the study group (^{b}p<0.05). c represents the comparison between the control group and the study group after treatment (^{c}p<0.05).

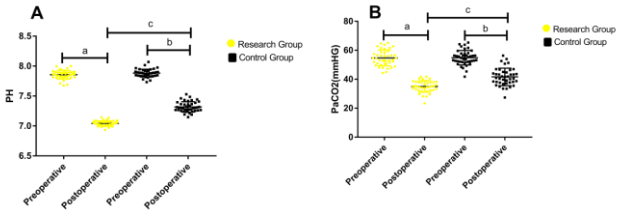

Figure 2. Comparison of blood gas indexes before and after treatment in two groups of patients. The description is given in the text.

Comparison of serum IL-6, TNF-α and CRP levels between the two groups before and after treatment

The levels of IL-6, TNF-α and CRP before and after treatment were observed. Before treatment, in the study group, the level of IL-6 was (103.62±24.04) ng/L, the level of TNF-α was (100.93±21.37) ng/L, and the level of CRP was (72.88±15.65) mg/L. In the control group, the IL-6 level was (102.74±23.48) ng/L, the TNF-α level was (99.83±21.43) ng/L, and the CRP level was (71.65±15.54) mg/L. There were no significant differences in IL-6, TNF-α and CRP levels between the two groups (all p>0.05). After treatment, in the study group, the IL-6 level of was (52.67±16.51) ng/L, the TNF-α level was (55.21±15.02) ng/L, and the CRP level was (31.21±9.12) mg/L. In the control group, the IL-6 level was (68.93±17.62) ng/L, the TNF-α level was (69.75±14.97) ng/L, and the CRP level was (38.12±8.65) mg/L. After treatment, the levels of IL-6, TNF-α and CRP in the two groups were lower than those before treatment (all p<0.05). The levels of IL-6, TNF-α and CRP in the study group were lower than those in the control group (all p<0.05). More details are shown in Figure 3. The description of each part of Figure 2 is as follows:

A: Comparison of IL-6 levels before and after treatment in two groups of patients: after treatment, the IL-6 levels of the study group were lower than that in the control group (all p<0.05). a represents the comparison before and after treatment in the control group (^{a}p<0.05). b represents the comparison before and after treatment in the study group (^{b}p<0.05). c represents the comparison between the control group and the study group after treatment (^{c}p<0.05).

B: Comparison of TNF-α levels before and after treatment in two groups of patients: after treatment, the TNF-α levels of the study group were lower than that in the control group (all p<0.05). a represents the comparison before and after treatment in the control group (^{a}p<0.05). b represents the comparison before and after treatment in the study group (^{b}p<0.05). c represents the comparison between the control group and the study group after treatment (^{c}p<0.05).

C: Comparison of CRP levels before and after treatment in two groups of patients: after treatment, the CRP levels of the study group was lower than that in the control group (all p<0.05). a represents the comparison before and after treatment in the control group (^{a}p<0.05). b represents the comparison before and after treatment in the study group (^{b}p<0.05). c represents the comparison between the control group and the study group after treatment (^{c}p<0.05).

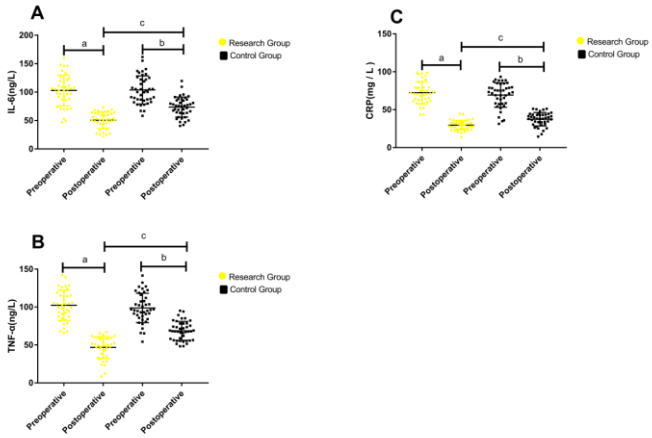

Figure 3. Comparison of serum IL-6, TNF-α and CRP levels between the two groups before and after treatment. The description is given in the text.

Comparison of bacterial clearance rates after treatment in both groups

The bacterial clearance rate after treatment was observed in the two groups. The bacterial clearance rate of the study group was 87.50%. The bacterial clearance rate of the control group was 68.29%. The difference was statistically significant (all p<0.05). More details are shown in Table 2.

Table 2. Bacterial clearance rates after treatment in both groups

Grouping	n	Clearance	Hypothetical clearance	Replacement	No clearance	Reinfection	Clearance rate
Study group	40	20	11	4	4	1	87.50%
Control group	41	14	9	5	6	7	68.29
F							4.322
p							0.038

Comparison of clinical effect between the two groups

The clinical effect was observed in the two groups. The total effective rate of the study group was 90.00%. The total effective rate of control group was 70.73%. The total effective rate of the study group was significantly higher than that of the control group (all $p<0.05$). More details are shown in Table 3.

Table 3. The clinical effect between the two groups

Grouping	Cure	Marked effect	Effective	Ineffective	Total effective rate
Study group	7	15	14	4	90.00
Control group	4	12	13	12	70.73
F					3.742
p					0.029

If the anti-inflammatory cytokines and pro-inflammatory cytokines in patients with severe pneumonia are out of balance, it will eventually form sepsis. Sepsis can cause loss of serious immune cells. Therefore, the number of peripheral blood lymphocytes in patients with sepsis is reduced, and the body is in a state of immune function inhibition. In recent years, Branco et al (16) pointed out that the immunosuppressive response in patients with sepsis has a very close relationship with lymphocytes.

Xuebijing is composed of five kinds of traditional Chinese medicine extracts, including Angelica sinensis, RhizomaLigusticiChuanxiong, Red peony root, Salvia and Safflower. It has the functions of promoting blood circulation, removing blood stasis and cooling blood expelling blood stasis (17). Basic research has confirmed that Xuebijing has the function of anti-inflammatory agents and regulates immune function (18, 19). Thymosin α1 is an immunoregulation drug that has the function of regulating the immune level of patients and inhibiting inflammatory reactions (20). Some studies have shown that good efficacy has been achieved in treating sepsis patients by thymosin α1 (21). Although the drug mechanism of Xuebijing and thymosin α1 is not exactly the same, both of them have the effect of inhibiting the inflammatory response and regulating immunity.

The results of this study showed that the temperature, respiration, heart rate, leukocytes and other general conditions of the patients in the study group were lower than those in the control group before and after treatment (all $p<0.05$). According to the observation of clinical efficacy, the total effective rate of the research group was significantly higher than that of the control group (all $p<0.05$). It suggested that the combination of the two drugs is more effective. According to relevant reports, the CRP level of patients with severe pneumonia complicated with sepsis is higher than that of normal people (22), which plays an important role in immunity and is the most important biomarker of infection and inflammation in disease and pathophysiological conditions (23). In our study, the levels of IL-6, TNF-α and CRP in the study group were significantly lower than those in the control group, indicating that the combination of the two drugs can effectively control the inflammatory response of patients and regulate immune function. At the same time, in the results of Chen et al (24), it was also suggested that Xuebijing significantly reduced the levels of inflammatory cells cytokines TNF-α and IL-6 in septic mice. Blood gas indexes before and after treatment and bacterial clearance rate after treatment were observed in the two groups. Before treatment, there was no significant difference in blood gas pH and PaCO2 between the two groups (all $p>0.05$). After treatment, the blood gas pH and PaCO2 levels of the two groups were lower than those before treatment (all $p<0.05$). Blood gas pH and PaCO2 levels in the study group were lower than those in the control group (all $p<0.05$). The bacterial clearance rate of the study group was significantly higher than that of the control group (all $p<0.05$), indicating that the two drugs could effectively alleviate the symptoms of patients and improve the blood gas condition of patients. and there was no serious adverse reaction during the treatment, and the safety was good.

In this study, blood gas indicators and inflammatory cytokines in the study group were lower than those in the control group after treatment. The reason for the analysis is that Xuebijing has the effect of promoting blood circulation, removing blood stasis, clearing away heat and eliminating pathogenic factors. It can inhibit the aggregation of blood platelet, accelerate blood flow, increase blood vascular tension and increase blood oxygen content. The clearance of hydrolase and protease can catalyze the enzyme by the production of bradykinin, repair creases of vascular endothelial cells, reduce vascular permeability, reduce exudation of inflammatory mediator and alleviate inflammatory symptoms in lesions (25). Moreover, thymosin α1 can directly stimulate the surface receptors of mononuclear macrophages and enhance their presenting of antigen and sterilization ability. Studies have shown that thymosin α1 can significantly improve the immune function of patients with sepsis and prevent the progression of inflammation (26).

However, due to the limited experimental conditions, this study still has some shortcomings. First of all, the base of research objects was small, which cannot be used for big data statistical analysis, and the experimental population was relatively single, which did not exclude the possibility of differences in other groups. Due to the use of consistency of drug in our hospital, it is not excluded that there may be differences in such drugs produced by other pharmaceutical factories. In addition, we speculate that the increase of inflammatory cytokines IL-6, TNF-α and CRP may also be caused by trauma or autoimmune diseases, which may affect our experimental results. Secondly, relevant data showed that thymosin α1 could reduce the mortality rate of sepsis, but we did not conduct prognostic follow-up in this study. We will follow up and investigate the research subjects in the future, and constantly improve and ameliorate our experiments to obtain the best experimental results.

Conclusions

In summary, thymosin α1 and Xuebijing injection can significantly improve the therapeutic effect of severe pneumonia complicated with sepsis, ameliorate the blood rheology status of patients, effectively remove bacteria and reduce the expression level of serum CRP, TNF-α, IL-6, IL-8 and other inflammatory factors in patients, which is worthy of clinical promotion.

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Interest conflict

None.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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