

Clinical Observations

A Clinical Study on the Effects and Mechanism of Xuebijing Injection (血必净注射液) in Severe Pneumonia Patients

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Objective: To observe the effects of Xuebijing Injection (血必净注射液) in patients with severe pneumonia, and to explore the mechanism.

Methods: Eighty cases of severe pneumonia are randomly assigned to the Xuebijing treatment (forty cases) and the control group (forty cases), with the same routine therapy provided in both groups. Clinical effective rates, inflammatory factors and organ function were observed in both groups.

Results: The effective rate was higher in Xuebijing group than that of the control group (80.0% vs. 67.5%, $P < 0.05$). As compared with the control group, the LDH, α 1-AG, α 1-AT levels and the peak body temperature decreased markedly with the Xuebijing treatment going, and the secretion of TNF- α , IL-6, IL-8 was suppressed in Xuebijing group; but no significant difference was found in leptin level.

Conclusion: Xuebijing Injection may show a protective effect in patients with severe pneumonia. The mechanism is possibly with the decreased secretion of TNF- α , IL-6, and IL-8.

Keywords: Xuebijing Injection; severe pneumonia; cytokine; acute phase reactants

Great progress has been achieved in antimicrobial therapeutics in recent years, yet severe pneumonia remains a major challenge in clinical treatment of pulmonary infection. The ageing society, increasing immuno-impaired hosts, diversifying pathogens as well as the rising drug resistance and other factors have lead to a rise of morbidity and mortality of severe pneumonia. Xuebijing Injection (血必净注射液 XBJ) is epurated from Chinese herbs, with satisfactory antiendotoxin and anti-inflammatory effects shown in clinical trials.^{1,2} The present study was designed to observe the effects of Xuebijing in patients with severe pneumonia and the influences on white blood cell (WBC), lactate dehydrogenase (LDH), peak body temperature (T_{max}) and acute phase reactants, and to explore the mechanism through detection of the cytokines.

METHODS

General Materials

The study evaluated the data in 80 patients with a confirmed diagnosis of severe pneumonia admitted at Respiratory Intensive Care Unit of PLA General Hospital from September 2007 to December 2009. The study was carried out with the approval from the Medical Ethics Committee of Chinese PLA General Hospital. Informed consent was obtained from all the study subjects. According to the definition formulated by American Thoracic Society in 2007, the patients with a past history of severe hepatic or renal dysfunction, rheumatic diseases, pulmonary fibrosis, tuberculosis or severe

malnutrition were excluded. These 80 patients were assigned with double-blind randomized clinical study to the Xuebijing treatment group (forty cases) and the control group (forty cases).

The data were comparable between the two groups with no significant differences in gender, age, duration of illness, clinical symptoms and signs and in the Acute Physiology and Chronic Health Evaluation II score as is presented in Table 1.

Treatment

Routine anti-microbial and sputum elimination agents were given to patients of both the two groups. Xuebijing Injection produced by Tianjin Hongri Pharmaceuticals Co. Ltd. was additionally used in the Xuebijing treatment, 50 ml of Xuebijing Injection with 100 ml of normal saline administered through intravenous drip twice a day. In order to enhance the therapeutic effects, Xuebijing Injection was given after the use of antibiotics. The treatment course was 14 days for both the two groups.

Criteria for Therapeutic Effects

The therapeutic effect is excellent if the symptoms of fever, cough, expectoration and dyspnea disappear, moist

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and dry rales of both lungs vanish, and the chest X ray shows normal in 14 days after the treatment. The effect is moderate if the above symptoms alleviate, moist and dry rales reduce, and the chest X-ray shows partial resorption of inflammation. The treatment is ineffective if the symptoms and signs are not improved or even deteriorated, and the chest X-ray reveals no resorption in 14 days.

Table 1. Baseline characteristics of the 80 patients involved in the study

Group		Control group (n=40)	Xuebijing group (n=40)
Gender	Male	23	25
	Female	17	15
Age	≤65years	21	19
	>65years	19	21
Duration	≤30 days	28	24
	>30 days	12	16
Comorbidities	Type 2 diabetes mellitus	3	5
	Coronary heart disease	5	5
	Hypertension	9	6
	Cerebrovascular disease	3	6
	Tracheotomy	3	4
	Mechanical ventilation	4	2
	Antibiotics	B-lactams/enzyme inhibitors	16
	Linezolid	7	5
	Quinolones	14	15
	Carbapenem	12	11
	Glycopeptides	2	1
	Fluconazole	6	8
APACHE II	≤25	22	19
	>25	18	21

Indexes Observed

The peak body temperature, WBC count, neutrophils (N), and the levels of serum LDH, C-reactive protein (CRP) were measured in patients of both the groups at baseline and on the 3rd, 7th and 14th day of treatment. By means of the enzyme linked immunosorbent assay, the levels of α_1 -acid glycoprotein (α_1 -AG), α_1 -antitrypsin (α_1 -AT), interleukin-6 (IL-6), interleukin-8 (IL-8) and tumor

necrosis factor (TNF- α) were detected, and the level of leptin was determined by radioimmunoassay.

Statistical Analysis

The Stata software 7.0 was used for statistical analysis. Parametric statistics, including student paired *t*-test and one-factor analysis of variance, is performed if the data accords with normal distribution and the variance is of homogeneity. Otherwise, nonparameter test, known as rank sum test, is performed instead. The data are expressed as mean \pm standard deviation, and $P < 0.05$ is considered significant.

RESULTS

Comparison of the Therapeutic Effects

1. Effective rates in the two groups

As shown in Table 2, the total effective rate in Xuebijing treatment group was markedly higher than that of the control group ($P < 0.05$).

2. Comparison of WBC, LDH and the peak body temperature

As compared with the baseline, the WBC, LDH and peak body temperature showed a markedly reducing tendency in both the groups (Table 3). WBC in both groups turned to normal on the 7th day. On the 14th day, the LDH level was significantly decreased in the Xuebijing treatment group, but no significant difference was found in the control group. The peak body temperature in the Xuebijing treatment group fell down to normal on the 3rd day, but it remained unchanged in patients of the control group on the 3rd day.

3. Comparison of the acute phase reactant levels (Table 4)

In patients of both groups, the serum CRP, α_1 -AG levels showed an obviously decreasing tendency as the treatment went on. On the 3rd day, CRP and α_1 -AG in the Xuebijing treatment group were significantly decreased, and lower than those in the control group ($P < 0.05$). In the control group, the concentration of α_1 -AT appeared to be ascending but consequently descending, whereas a notable decrease of α_1 -AT was found in the Xuebijing treatment group ($P < 0.05$). Generally speaking, as compared with the control group, the serum CRP, α_1 -AG and α_1 -AT levels in patients of the Xuebijing treatment group were decreased earlier and more obviously ($P < 0.05$).

Table 2. Comparison of the effective rates in the two groups of patients with severe pneumonia

Group	Cases	Excellent	Moderate	Inefficient	Total effective rate (%)
Xuebijing	40	15	17	8	80.0*
Control	40	12	15	13	67.5

Note: As compared with the control group, * $P < 0.05$.

Table 3. Comparison of WBC, N, LDH and the peak body temperature in the two groups of patients with severe pneumonia (cases=40)

Item	Group	Baseline	3rd day	7th day	14th day
WBC ($10^9/L$)	XBJ	15.90±8.50	10.90±5.40	8.40±3.60*	5.70±1.90* [#]
	Control	13.10±6.00	10.50±4.50	9.30±4.10*	8.10±2.50*
N (%)	XBJ	0.81±0.13	0.80±0.11	0.82±0.11	0.75±0.13
	Control	0.82±0.10	0.78±0.13	0.80±0.11	0.72±0.18*
LDH (U/L)	XBJ	444.00±354.00	413.00±185.00	392.00±229.00	253.00±89.00*
	Control	316.00±210.00	307.00±177.00	283.00±134.00	238.00±119.00
Tmax (°C)	XBJ	37.60±1.10	36.90±0.70*	36.90±0.60*	36.80±0.80*
	Control	37.50±1.20	37.10±0.80	36.90±0.70	36.80±0.80

Notes: * $P < 0.05$, as compared with the baseline; [#] $P < 0.05$ as compared with the control group.

Changes in the Levels of Cytokines

As shown in Table 5 the serum IL-6 level was reduced in both the two groups as the treatment went on. On the 3rd day, the IL-6 level in patients of the Xuebijing treatment group was obviously decreased as compared with the control group ($P < 0.05$). The serum TNF- α and

IL-8 level were elevated the treatment went on; whereas no significant changes were observed in Xuebijing group, TNF- α and IL-8 were markedly lower than the control group respectively on the 7th day and the 14th day. The leptin level showed no obvious change as compared with the baseline in both the groups.

Table 4. Comparison of the acute phase reactant levels in the two groups of patients with severe pneumonia (cases=40)

Marker	Group	Baseline	3rd day	7th day	14th day
CRP (mg/dL)	XBJ	13.63±8.95	6.08±4.01* [#]	6.06±4.22*	4.69±3.82*
	Control	10.35±6.40	10.16±4.15	6.06±4.22*	4.69±3.82*
a1-AG (ug/mL)	XBJ	583.00±195.5	464.90±113.00* [#]	345.60±59.10* [#]	353.00±99.90*
	Control	591.90±92.8	567.10±128.10	437.30±111.10*	330.80±95.40*
a1-AT (mg/mL)	XBJ	2048.00±610.90	2005.00±676.00* [#]	1216.00±506.00* [#]	730.00±212.70* [#]
	Control	1946.00±1232.00	2826.00±1238.00*	2108.00±929.40	1633.00±746.60*

Notes: * $P < 0.05$, as compared with the baseline; [#] $P < 0.05$, as compared with the control group.

Table 5. Comparison of the cytokine levels (IL-6, IL-8, TNF-a, Leptin) of patients with severe pneumonia

Marker	Group	Baseline	3rd day	7th day	14th day
IL-6 (ng/mL)	XBJ	0.04±0.01	0.02±0.01* [#]	0.02±0.00*	0.02±0.01*
	Control	0.03±0.02	0.03±0.01	0.02±0.01*	0.02±0.01*
IL-8 (ng/mL)	XBJ	0.32±0.12	0.31±0.11	0.32±0.18	0.32±0.13 [#]
	Control	0.31±0.18	0.24±0.15	0.48±0.46*	0.47±0.22*
TNF-a (pg/mL)	XBJ	20.05±9.63	22.91±11.29	20.73±11.32 [#]	21.97±11.14
	Control	21.71±7.65	29.72±19.06	32.49±16.71*	30.67±13.19
Leptin (ng/mL)	XBJ	10.15±6.31	10.06±9.00	11.40±8.22	13.01±9.86
	Control	10.19±6.63	13.49±6.65	11.83±4.89	12.62±8.89

Notes: * $P < 0.05$, as compared with baseline; [#] $P < 0.05$, as compared with the control group.

DISCUSSION

The pathogenesis of severe pneumonia is related with infection, toxin and the immunological factors, which consequently cause damage to the lung tissues. Among these factors, bacterial infection is the main cause for deterioration of pneumonia, but the use of antibiotics alone may not show good results. Some medical literature have reported that the combined use of herbal medicines for clearing the toxic heat, and expelling the sputum may help alleviate the stress reaction, accelerate the toxin elimination, and improve the respiratory function. Xuebijing Injection is a compound preparation

of Chinese medicine with the efficacy of activating blood circulation to remove blood stasis, cooling the blood and clearing the toxic heat, which is composed of Chishao (Radix Paeoniae Rubra), Danggui (Radix Angelica Sinensis), Chuanxiong (Rhizoma Chuanxiong), Honghua (Flos Carthami), and Danshen (Radix Salviae Miltiorrhizae).

The present study shows that the use of antibiotics in combination with Xuebijing injection can notably decrease the serum LDH level, lower the daily peak body temperature, decline the acute phase reactants (CRP,

α_1 -AG and α_1 -AT), and enhance the total effective rate in severe pneumonia patients. The secretion of TNF- α , IL-6 and IL-8 in Xuebijing-treated patients was obviously suppressed as compared with the control group, but with no significant influence on the release of leptin. The main pathogenic bacteria in severe pneumonia are Gram negative, like *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Escherichia coli*, etc. Lipopolysaccharide (LPS), a bioactive substance, exists in the adventitia of cell wall of the Gram negative bacterial, which is the main inducing substance for systemic inflammatory response syndrome (SIRS) and sepsis.^{3,4} Many researches have demonstrated that antibiotics can drive releasing of LPS while killing the bacteria, and LPS may consequently stimulate the macrophages to produce more inflammatory mediators, leading to deterioration of bacterial infection, or even SIRS and/or sepsis.^{5,6} Among the inflammatory factors, TNF- α , IL-6 and IL-8 are the most influential, because they take part in the initial onset of SIRS, known as the pre-inflammatory mediators; Stimulate to produce more secondary inflammatory mediators, and induce the synthesis of acute phase reactants like CRP, α_1 -AG and α_1 -AT in the liver. This study showed that secretion of TNF- α , IL-6 and IL-8 was suppressed on the 3rd, 7th and 14th day after Xuebijing treatment, indicating that Xuebijing Injection may exert anti-endotoxin effects by blocking the uncontrolled release of endogenous inflammatory mediators like TNF- α , IL-6 and IL-8; as a result, the vicious cycle of inflammation onset is interrupted, the overactive inflammatory reactions are suppressed, the development of SIRS is blocked; meanwhile, the acute phase reactants are reduced, and the clinical symptoms are relieved, which conform to the results of many studies reported both at home and abroad.^{7,8} Leptin is a protein product encoded by fat gene. It has the effects on body weight regulatory circuit and feedback regulation of energy metabolics, it can also act as a cytokine to induce generation, differentiation and enhancement of hematopoietic cells, and provide monocytes with nutrition, enhance the generation and phagocytosis actions of mononuclear macrophages, stimulate the secretion of pre-inflammatory and anti-inflammatory substances in monocytes, activate the vascular regeneration, and strengthen the body

resistance.⁹ Through observation of the influence of Xuebijing on leptin releasing, the study tries to explore whether the effect of Xuebijing is related with the enhancement or inhibition of leptin release. The results from the present study shows that Xuebijing has no significant influence on leptin release, possibly the secretion and regulation of leptin are influenced by lots of factors, among which the body weight and insulin level are the key factors.

To sum up, Xuebijing Injection can effectively regulate the inflammatory factors, alleviate the symptoms and various inflammation reactions in severe pneumonia, without obvious adverse side effects on the organ functions, and biochemical indexes.

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