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Original Article

The effect of Xuebijing on the inflammation and pulmonary function of severe pneumonia patients treated by bronchoalveolar lavage under fiberoptic bronchoscopy

Hong Li[1], Shijia Xu[2], Zhouyong Gang[3], Yang Chen[1], Hongmei Yang[1], Lili Luo[1], Fei Wang[1]

[1]Department of Emergency, The First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine, Guiyang 550001, Guizhou Province, China; [2]Department of Cardiology, Guiyang Second People's Hospital, Guiyang 550009, Guizhou Province, China; [3]Department of Cardiology, Guangxi Medical University, Nanning 530000, Guangxi Province, China

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Abstract: Objective: To explore the clinical efficacy and safety of Xuebijing (XBJ) combined with bronchoalveolar lavage (BAL) under fiberoptic bronchoscopy in the treatment of severe pneumonia. Methods: A total of 76 patients with severe pneumonia treated at the first affiliated Hospital of Guangxi Medical University from September 2017 to June 2019 were enrolled in the study and assigned to a monotherapy group (n=42) or a combination group (n=36) according to the treatment method each received. The patients in the monotherapy group were treated with BAL under fiberoptic bronchoscopy based on the routine treatment, while those in the combination group were treated with XBJ in addition to the treatment the monotherapy group received. The two groups were compared in terms of the clinical efficacy, the disappearance of their clinical symptoms, the improvement in their pulmonary function and arterial blood gas indexes, and their inflammatory index levels. Moreover, the adverse reactions of the two groups were evaluated. Results: The total markedly effective rate of the combination group was higher than it was in the monotherapy group, and the combination group experienced an earlier disappearance of the main clinical symptoms, including pulmonary rales, hyperthermia, cough, and thoracodynia (all $P<0.05$). In addition, after the treatment, the pulmonary function indexes in the combination group were better than they were in the monotherapy group (all $P<0.05$), and the C-reactive protein (CRP), interleukin-1β (IL-1β), and interleukin-6 (IL-6) levels in the combination group were all lower than they were in the monotherapy group (all $P<0.05$). Moreover, the adverse reactions in the two groups were similar and showed no significant differences ($P>0.05$). Conclusion: XBJ in addition to routine treatment and BAL done using fiberoptic bronchoscopy can safely and effectively treat patients with severe pneumonia, improve their arterial blood gas indexes and pulmonary function, and alleviate their inflammatory response.

Keywords: Xuebijing, bronchoalveolar lavage under fiberoptic bronchoscopy, severe pneumonia, efficacy

Introduction

Pneumonia is a prevalent clinical respiratory disease and is also a common cause of hospitalization and death [1]. Severe pneumonia is a serious form of pneumonia, and it refers to severe hypoxemia or acute respiratory failure requiring ventilatory support in patients with pneumonia, or circulatory failure such as hypotension and shock and other organ dysfunction in such patients [2]. Although there are many treatment options for patients with severe pneumonia [3], their mortality rate in intensive care units (ICUs) is still as high as 29-47% [4]. Therefore, finding a more effective treatment for severe pneumonia has long been a focus of clinical research.

Xuebijing (XBJ) is a Chinese patent medicine composed of safflower, red peony root, rhizoma chuanxiong, *Salvia miltiorrhiza*, as well as *Angelica sinensis*. It has been used in China for more than ten years and has been verified to have the functions of antagonizing endotoxin, resisting inflammation, relieving oxidative stress, regulating immunity, and improving microcirculation and blood coagulation [5, 6]. In China, XBJ has been widely used in the treat-

ment of sepsis and other inflammatory diseases, and it has demonstrated good therapeutic effects [7]. Several clinical studies have verified that XBJ can treat patients with severe pneumonia safely and effectively [8, 9]. Bronchoalveolar lavage (BAL) is a new technology developed on the basis of fiberoptic bronchoscopy, which can quickly and effectively remove airway mucus, improve airway ventilation, and make inhaled drugs directly contact the airway walls to alleviate airway inflammation [10]. A previous study revealed that bronchoalveolar lavage based on mechanical ventilation can improve the treatment effect in patients with severe pulmonary infections, improve the patients' blood gas indexes, and alleviate their inflammation [11].

Both XBJ and BAL can benefit patients in severe condition, but as far as we know, there is no clinical data on XBJ combined with BAL under fiberoptic bronchoscopy in the treatment of severe pneumonia. Therefore, we designed this study to explore the clinical efficacy and safety of XBJ combined with BAL under fiberoptic bronchoscopy in the treatment of severe pneumonia.

Materials and treatment

Research participants

A total of 76 patients with severe pneumonia admitted to the first affiliated Hospital of Guangxi Medical University from September 2017 to June 2019 were enrolled in the study and assigned to a monotherapy group (n=42) or a combination group (n=36) according to the treatment method each patient received. Inclusion criteria: Patients meeting the diagnostic criteria for severe pneumonia [12]. Exclusion criteria: Patients who are pregnant or lactating, patients unable to communicate normally, patients without complete clinical data, patients allergic to the drugs used in this study, and patients with comorbid severe organ dysfunction such as of the heart, brain, or kidneys. All the patients signed informed the consent forms, and this study was approved by the ethics committee of our hospital.

Treatment methods

The patients in both groups were given routine treatment against severe pneumonia, such as anti-infection treatment, mechanical ventilation to keep the respiratory tract unobstructed, and corresponding nutritional support.

The patients in the monotherapy group were given BAL under fiberoptic bronchoscopy based on the routine treatment as follows: Each patient was required to fast for 6 hours before treatment, and then each was treated with midazolam. Subsequently, fiberoptic bronchoscopy was adopted to reach the lesion on the bronchus and the affected side through an endotracheal intubation tube to suck the airway secretions out under negative pressure. Afterwards, the lesion site was lavaged with a 0.9% sodium chloride solution at 37°C repeatedly 3-5 times (10-20 mL sodium chloride solution each time) until the aspirate was clear. The total amount of lavage fluid was 100 mL or less.

The patients in the combination group were additionally treated with an XBJ injection in addition to the treatment the monotherapy group received as follows: 100 ml XBJ injection was diluted to 200 mL with saline as a solvent, and each patient was given 200 ml of the diluted solution through an intravenous drip twice each day, for 7 consecutive days.

Outcome measures

The clinical efficacy of each patient was evaluated on the final day of the treatment: Cured: Disappearance of the cough and fever, a normal white blood cell count and classification, and the absorption of the pulmonary lesions >90%. Markedly effective: Significant alleviation of the cough and fever, a normal white blood cell count and classification, and the absorption of the pulmonary lesions >50%. Effective: Partial alleviation of the cough and fever, a normal white blood cell count and classification, and the absorption of the pulmonary lesions <50%. Ineffective: not in conformance with the above criteria. The total markedly effective rate = (The number of cured patients + the number of markedly effectively treated patients)/the total number of patients * 100%.

The time to the disappearance of the main clinical symptoms (pulmonary rales, hyperthermia, cough, as well as thoracodynia), the length of the hospital stays, and the mechanical ventilation times of the two groups were recorded.

Table 1. A comparison of the general data in the two groups [n (%)] ($\bar{x}$ ± sd)

Group	The monotherapy group (n=42)	The combination group (n=36)	χ^2/t	P
Sex			0.339	0.560
Male	29 (69.05)	27 (75.00)		
Female	13 (30.95)	9 (25.00)		
Place of residence			0.126	0.722
Urban area	24 (57.14)	22 (61.11)		
Rural area	18 (42.86)	14 (38.89)		
Smoking history			1.381	0.240
Yes	25 (59.52)	27 (72.22)		
No	17 (40.48)	10 (27.78)		
Age (Y)	55.25±8.56	54.96±7.23	0.160	0.873
Weight (kg)	63.21±4.75	62.24±3.18	1.041	0.301
Course of disease (d)	1.12±0.79	1.21±0.68	0.595	0.595
Heart rate (times/min)	86.86±5.88	87.51±6.15	0.477	0.635

The pulmonary function indexes and the arterial blood gas indexes of the two groups at one day before the treatment and at the final day of treatment were measured using a pulmonary function detector and a blood gas analyzer, respectively. The pulmonary function indexes included forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and FEV_1/FVC. The arterial blood gas indexes included arterial partial pressure of oxygen (PaO_2), arterial partial pressure of carbon dioxide (PCO_2), and arterial oxygen saturation (SpO_2).

Fasting venous blood was sampled from each patient in the two groups before the treatment and on the final day of the treatment, and the sampled blood was centrifuged to collect the serum. Subsequently, the inflammatory factors including C-reactive protein (CRP), interleukin-1β (IL-1β), and interleukin-6 (IL-6) in the serum were quantified using an enzyme-linked immuno-sorbent assay (ELISA) with the corresponding ELISA kits purchased from the Abcam Company, United States, following the kit's instructions.

Statistical analyses

In this study, the statistical analysis was carried out using SPSS 19.0, and the data were visualized into the required figures using GraphPad Prism 7. The enumeration data were compared between the groups by chi-square tests. The measurement data were compared between the groups using independent sample T tests, the data were compared within the groups before and after the treatment using paired t tests, and the data was compared among groups using one-way ANOVA. The statistical values were verified using back testing. $P<0.05$ indicated a significant difference.

Results

A comparison of the clinical data

There was no significant difference between the two groups in terms of the general clinical data, including sex, place of residence, smoking history, age, weight, course of disease, or heart rate (all $P>0.05$) **Table 1**.

A comparison of the clinical efficacy

According to evaluation of the two groups' clinical efficacy, the monotherapy group showed a total markedly effective rate of 73.81%, with 11 cured patients (26.79%), 20 markedly effectively treated patients (47.62%), 5 effectively treated patients (11.90%), and 6 ineffectively treated patients (14.29%), while the combination group showed a total markedly effective rate of 91.67%, with 16 cured patients (44.44%), 17 markedly effectively treated patients (47.22%), 1 effectively treated patient (2.78%), and 2 ineffectively treated patients (5.56%), so the total markedly effective rate of the monotherapy group was higher than rate of the monotherapy group ($P<0.05$) **Table 2**.

A comparison of the times to the disappearance of the clinical symptoms, the hospitalization times, and the mechanical ventilation times

According to our observations of the times to the disappearance of the main clinical symptoms in the two groups, the combination group experienced an earlier disappearance of the

Table 2. A comparison of the clinical efficacy [n (%)]

Group	Cured patients	Markedly effectively treated patients	Effectively treated patients	Ineffectively treated patients	Total marked effective rate
The monotherapy group (n=42)	11 (26.79)	20 (47.62)	5 (11.90)	6 (14.29)	31 (73.81)
The combination group (n=36)	16 (44.44)	17 (47.22)	1 (2.78)	2 (5.56)	33 (91.67)
χ^2	-	-	-	-	4.197
P	-	-	-	-	0.041

Table 3. Comparisons of the disappearance times of the clinical symptoms and the hospitalization times in the two groups after the treatment ($\bar{x} \pm sd$)

Group	The monotherapy group (n=42)	The combination group (n=36)	t	P
Pulmonary rales (d)	2.91±0.86	2.27±0.95	3.078	0.003
Hyperthermia (d)	2.27±1.05	1.56±1.16	2.797	0.007
Cough (d)	5.45±1.22	4.15±1.14	4.755	<0.001
Thoracodynia (d)	3.26±1.17	2.42±0.99	3.330	0.001
Hospitalization time (d)	19.56±3.72	15.76±3.52	4.535	<0.001
Mechanical ventilation time (d)	8.23±2.45	6.17±2.38	3.691	<0.001

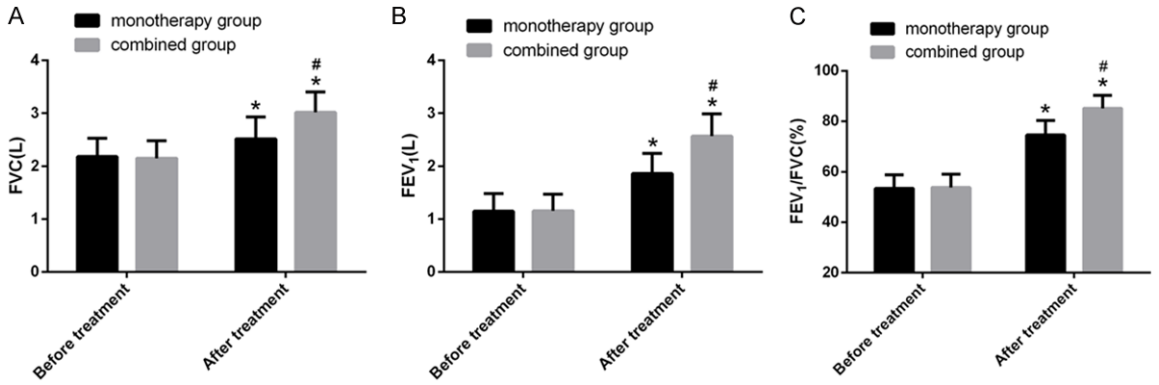

Figure 1. A comparison of the pulmonary function indexes. A. Comparison of the FVC changes between the two groups before and after the treatment. B. Comparison of FEV_1 changes between the two groups before and after the treatment. C. Comparison of FEV_1/FVC changes between the two groups before and after the treatment. Notes: * indicates compared with the same group before the treatment, $P<0.05$; # indicates compared with the monotherapy group after the treatment, $P<0.05$.

main clinical symptoms including pulmonary rales, hyperthermia, cough, and thoracodynia than the monotherapy group did (all $P<0.05$), and the combination group also experienced shorter hospitalization times and mechanical ventilation times than the monotherapy group (both $P<0.05$) **Table 3**.

A comparison of the pulmonary function indexes

The quantification of the pulmonary function indexes in the two groups before and after the treatment showed that after the treatment, the FVC, FEV_1, and FEV_1/FVC levels in both groups were improved, and the three indexes in the combination group were all better than those of the monotherapy group (all $P<0.05$) **Figure 1**.

A comparison of the arterial blood gas indexes

The quantification of the arterial blood gas indexes in the two groups before and after the treatment showed that after the treatment, the PaO_2, $PaCO_2$, and SpO_2 levels in both groups were improved, and the three indexes in the

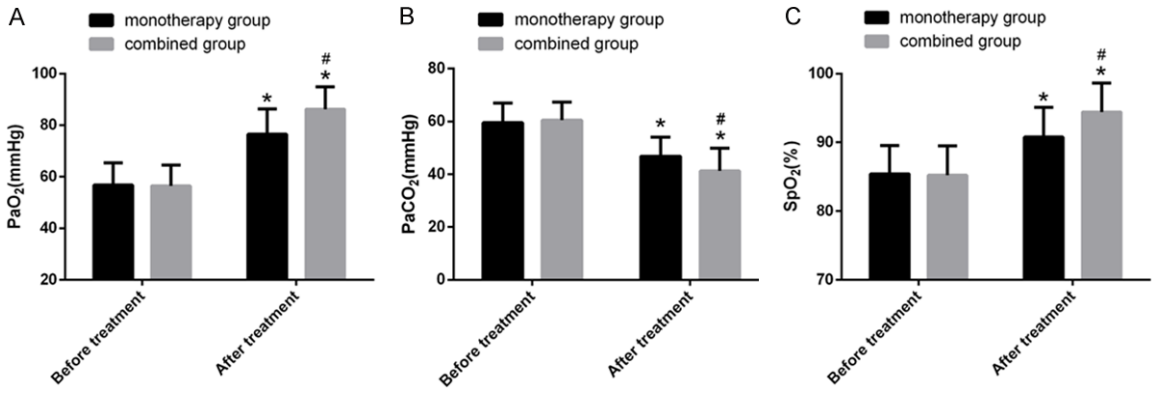

Figure 2. A comparison of the arterial blood gas indexes. A. Comparison of the PaO_2 changes between the two groups before and after the treatment. B. Comparison of the $PaCO_2$ changes between the two groups before and after the treatment. C. Comparison of the SpO_2 changes between the two groups before and after the treatment. Notes: * indicates compared with the same group before the treatment, $P<0.05$; # indicates compared with the monotherapy group after the treatment, $P<0.05$.

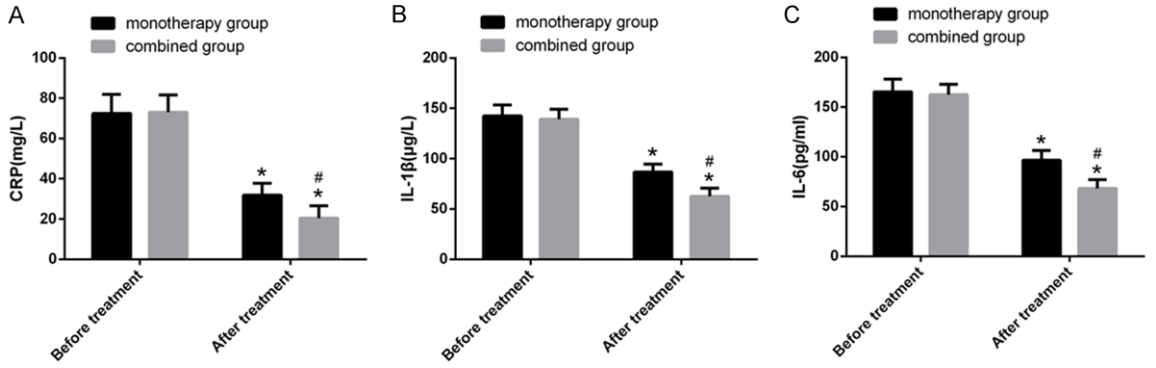

Figure 3. A comparison of the inflammatory indexes. A. Comparison of the CRP changes between the two groups before and after the treatment. B. Comparison of IL-1β changes between the two groups before and after the treatment. C. Comparison of IL-6 changes between the two groups before and after the treatment. Notes: * indicates compared with the same group before the treatment, $P<0.05$; # indicates compared with the monotherapy group after the treatment, $P<0.05$.

combination group were all better than they were in the monotherapy group (all $P<0.05$) **Figure 2**.

A comparison of the inflammatory indexes

The measurement of the inflammatory indexes in the two groups before and after the treatment showed that after the treatment, the CRP, IL-1β, and IL-6 levels in both groups declined, and the levels of the three indexes in the combination group were lower than they were in the monotherapy group (all $P<0.05$) **Figure 3**.

Occurrence of adverse reactions

Adverse reactions occurred in both groups, but there was no significant difference between the two groups ($P>0.05$) **Table 4**.

Discussion

This study mainly determined the clinical efficacy and safety of XBJ based on routine treatment and BAL under fiberoptic bronchoscopy in the treatment of severe pneumonia. It was found that the addition of XBJ contributed to better clinical efficacy in patients with severe pneumonia and can improve patients' pulmonary and ventilation functions and relieve their inflammatory reactions, without causing too many adverse reactions.

Severe pneumonia, a common disease in the ICU, often involves multiple organs. Characterized by its severe status, rapid progression, and high mortality, it poses a serious threat to people's lives and health [13, 14]. As the main drug for severe pneumonia, antibiot-

Table 4. The occurrence of adverse reactions [n (%)]

Group	The monotherapy group (n=42)	The combination group (n=36)	χ^2	P
Dizziness and hypodynamia	1 (2.38)	2 (5.56)	0.528	0.467
Nausea and vomiting	2 (4.76)	2 (5.56)	0.025	0.874
Arrhythmia	1 (2.38)	1 (2.78)	0.012	0.912
Chest distress	1 (2.38)	1 (2.78)	0.012	0.912
Rash	1 (2.38)	3 (8.33)	1.412	0.235
Total number of people affected	5 (11.90)	9 (25.00)	2.653	0.103

ics can effectively control the progression of the disease, but with the abuse of antibiotics, the drug resistance of patients becomes increasingly serious, which gradually increases the difficulty of treatment [15]. In addition, there is still a lack of standard treatment for severe pneumonia at this stage. Therefore, it is urgent to find a more effective treatment plan. XBJ is a Chinese patent medicine developed from many Chinese herbal medicines. It can treat many diseases including sepsis, urethritis, cystitis, tonsillitis, and pneumonia. In China, XBJ has been used clinically for more than ten years, and about 800,000 patients receive XBJ-based treatment every year [16]. BAL, which is based on fiberoptic bronchoscopy, has been widely adopted in clinical practice, because it can thoroughly remove inflammatory secretions in the respiratory tract by lavage and aspiration and realize a local purification to ensure the ideal drug concentration in local lesions and can also promote gas exchange, thus improving patients' respiratory function [17, 18]. However, the clinical efficacy and safety of XBJ based on routine treatment and BAL under fiberoptic bronchoscopy in the treatment of severe pneumonia still lacks effective clinical data. Therefore, we designed this study. It was found that the total markedly effective rate of the combination group was higher than it was in the monotherapy group, and the combination group experienced an earlier disappearance of the main clinical symptoms, including pulmonary rales, hyperthermia, cough, and thoracodynia than the monotherapy group did, and the combination group also experienced shorter hospitalization times and mechanical ventilation times than the monotherapy group. Because of the inflammatory response, the inflammatory secretions will settle on the airway walls of patients with pneumonia, thereby resulting in shortness of breath in the patients. The results of arterial blood gas analysis can directly reflect the acid-base balance and hypoxia degree, which are related to the severity of patients with severe pneumonia [19]. We determined the arterial blood gas indexes and pulmonary function indexes in the patients in the two groups and found that after treatment, both the arterial blood gas indexes and pulmonary function indexes of the combination group were better than those of the monotherapy group, which indicated that XBJ based on routine treatment and BAL under fiberoptic bronchoscopy was effective in treating severe pneumonia. Then, we compared adverse reactions between the two groups, and found that the adverse reactions in the two groups were similar, and there was no significant difference between the two groups, which implied that XBJ based on routine treatment and BAL is safe.

Studies have shown that endotoxin generated by bacteria in patients with pneumonia can stimulate nuclear macrophages, endothelial cells, and neutrophils to produce a large number of inflammatory mediators, resulting in an unbalanced inflammatory response in the body and thus damaging patients' tissues and organs [20, 21]. Therefore, anti-inflammation is a main direction of treating pneumonia. Procalcitonin (PCT) is a calcitonin propeptide. Its concentration in the blood is extremely low under normal physiological conditions, but its serum level will increase significantly when the human body is in a severe situation [22]. IL-1β and IL-6 are two common pro-inflammatory factors. Their levels in patients with inflammatory diseases will increase, and they can reflect the severity of the inflammatory response [23, 24]. In this study, after the treatment, the serum CRP, IL-1β, and IL-6 levels in both groups declined significantly, and their levels in the combination group were lower than they were

in the monotherapy group, This finding is similar to the research results of Qi et al. [9] who found that XBJ can reduce the release of inflammatory cytokines such as TNF-α, IL-6, and IL-8. It also suggests that XBJ may be able to treat severe pneumonia by reducing the release of inflammatory cytokines. These results may be due to the fact that XBJ can reduce the stimulation of endotoxin on nuclear macrophages, endothelial cells, and neutrophils by lowering the level of the endotoxins produced by bacteria, thus reducing the production of inflammatory mediators.

There are some limitations to this study. First of all, the research participants were all selected from the same region, so the results are regional to a certain extent, which may affect the promotion of the treatment scheme in other regions. Secondly, we only analyzed patients aged 18-75 years, but did not explore whether XBJ had the same superior effect on patients under 18 years or over 75 years old. In addition, we did not analyze the cost of XBJ combined with BAL under fiberoptic bronchoscopy from an economic point of view. We also did not explore the efficacy or safety of XBJ alone in the treatment of severe pneumonia. It is hoped that the above limitations can be addressed in future clinical research.

To sum up, XBJ based on routine treatment and BAL under fiberoptic bronchoscopy can safely and effectively treat patients with severe pneumonia, improve their arterial blood gas indexes and pulmonary function, and alleviate their inflammatory response.

Disclosure of conflict of interest

None.

Address correspondence to: Shijia Xu, Department of Cardiology, Guiyang Second People's Hospital, No. 547 Jinyang South Road, Guanshan Lake District, Guiyang 550009, Guizhou Province, China. Tel: +86-17785005430; E-mail: shijiaxu12@163.com

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