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Original Article

Ulinastatin plus biapenem for severe pneumonia in the elderly and its influence on pulmonary function and inflammatory cytokines

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Abstract: To estimate the efficacy of ulinastatin (UTI) plus biapenem (BIPM) in the treatment of severe pneumonia in the elderly and its influence on pulmonary function (PF) and inflammatory cytokines. Methods: We included 97 elderly patients with severe pneumonia in the present study. Patients in control group (n=47) were given BIPM, and those in research group (n=50) were treated with BIPM plus UTI. The clinical efficacy, adverse reactions, arterial blood gas (ABG) indices, PF and inflammatory cytokines were recorded. Results: Patients in the research group had earlier fever clearance, inflammation absorption and cough disappearance than those in control group, as well as better clinical efficacy. In addition, no significant differences were found in the incidence of adverse reactions between the two groups during treatment. Monitoring changes in ABG indices, PF, and inflammatory cytokines revealed increased levels of PaO_2, pH, FEV1, FVC, FEV1/FVC after treatment, but levels of $PaCO_2$, IL-1β, IL-6, TNF-α, and hs-CRP decreased compared to before treatment. Levels of indices that increased after treatment in the research group were higher than those in the control group, whereas the levels of other indices that decreased after treatment were lower. Conclusion: The combination of UTI and BIPM shortens the time of symptom disappearance, enhances PF, and inhibits inflammation, achieving higher efficacy in the treatment of severe pneumonia in the elderly.

Keywords: Severe pneumonia, elderly patients, ulinastatin, biapenem

Introduction

Pneumonia is an infectious type of inflammation, including pathogen infection, of the lungs in human beings; it has a specific incubation period and is responsible for most hospitalization deaths in patients with lower respiratory infection and over 65 years old [1]. A decline in immunity of elderly patients contributes to the coexistence of multiple underlying diseases and the enhancement of bacterial resistance, so the elderly are more likely to develop severe pneumonia [2]. Among all hospitalized patients with community-acquired pneumonia, 10%-22% suffer from severe pneumonia and need intensive care; however, severe pneumonia is progressing rapidly, with a fatality rate as high as 50% [3]. Therefore, it is imperative to treat this disease quickly and effectively.

Old age is associated with the decline of immune function, which usually leads to immune aging, low-grade systemic inflammation and weakened response to immune stimulation, resulting in a long-term inflammatory state of the body [4]. During the progression of severe pneumonia, excessive release of inflammatory mediators stimulated by infection induces inflammatory reactions in the lungs and the body, damaging the lungs of patients [5]. Ulinastatin (UTI) is a broad-spectrum trypsin inhibitor extracted from human urine, and it can remove oxygen free radicals, stabilize lysosomal membranes, and inhibit inflammatory substances [6]. Biapenem (BIPM) is commonly used in patients with severe infections because it exhibits broad-spectrum antibacterial activity and is able to kill pathogenic microorganisms; however, the therapeutic effect of BIPM monotherapy is not promising [7]. BIPM has been confirmed to have good tolerance and efficacy in respiratory tract and urinary tract infections [8]. UTI is conducive to alleviate burn-wound edema and protecting multiple organs of patients with severe burns. Despite the inhibi-

tory effect of both UTI and BIPM on inflammation [9, 10], the efficacy of their combination in elderly patients with severe pneumonia has rarely been investigated.

In the present study, we used the combination therapy of UTI and BIPM to treat elderly patients with severe pneumonia to estimate its clinical efficacy.

Materials and methods

Clinical data

Ethics approval was granted from the hospital Committee. All patients were informed and signed the consent form. Ninety-seven elderly patients with severe pneumonia admitted to The First Hospital of Kunming from January 2020 to November 2020 were included. Inclusion criteria: patients meeting the diagnostic criteria of severe pneumonia developed by the American Thoracic Society and Infectious Diseases Society of America [11]; patients receiving no anticoagulants 15 days before treatment; patients aged ≥65 years old; patients with complete clinical data; patients who tested positive in sputum cultures. Exclusion criteria: patients complicated with malignant tumor, heart disease, severe organ dysfunction, coagulation dysfunction, pulmonary tuberculosis, severe systemic infection, mental disease, or cerebrovascular hemorrhage; patients allergic to any drugs adopted in this study.

Grouping and administration

Patients were given basic treatment of phlegm resolution, fever reduction, ventilation, maintenance of electrolyte balance and acid-base balance [12]. On this basis, the control group (n=47) was given intravenous drip of 0.3 g BIPM (specification: 0.3 g; H20140120; Luoxin Pharma, Shandong, China) dissolved in 100 mL normal saline, 0.6 g daily, twice per day, 30-60 min each time. The research group (n=50) was treated with intravenous drip of 250,000 U ULI (specification: 100,000 IU; H19990134; Techpool Pharma, Guangdong, China) dissolved in 100 mL normal saline, twice a day. All patients were treated for 14 consecutive days.

Efficacy criteria

The efficacy of treatment in each group was evaluated [13]. Cured: symptoms and physical signs disappeared, and X-ray demonstrated complete disappearance of lung lesions. Markedly effective: symptoms and physical signs almost disappeared, and X-ray demonstrated significant absorption of lung lesions. Effective: symptoms and physical signs were alleviated, and partial absorption of lung lesions was observed. Ineffective: symptoms and physical signs did not disappear, or even worsened, and lung lesions were not absorbed, or aggravated. (cured + markedly effective + effective cases)/total cases × 100% = overall response rate.

Outcome measures

The fever clearance time, inflammation absorption time and cough disappearance time were recorded. Any adverse reactions including nausea, vomiting, skin rash, diarrhea and pruritus were observed during treatment.

Arterial blood gas (ABG) indices ($PaCO_2$, PaO_2, arterial pH) were measured by the EasyStat Blood Gas Analyzer (Medica, Suzhou, China). And PF parameters (FEV1, FVC and FEV1/FVC) were tested by the S-980A I tester before and after treatment. IL-1β, IL-6, TNF-α and hs-CRP levels in serum were quantified by ELISA (Hengfei Biotech, Shanghai, China) with the Varioskan LUX multimode reader (Thermo Fisher, Shanghai, China), details were shown in Li's report [14].

Statistical methods

Mean ± Standard Deviation (SD) was used to standardize the data. Quantitative data with a normal distribution were analyzed by independent samples student's t test, and intra-group comparisons were conducted with paired t test. Categorical data were expressed by [n (%)], and inter-group comparisons were conducted by Chi-square test. Statistical significance was set at $P < 0.05$. SPSS 20.0 (IBM Corp., Armonk, New York, USA) and GraphPad Prism 6.0 (Turntech, Beijing, China) were used for statistical processing and graphing, respectively.

Results

General data

Patients in the two groups were comparable for general data including course of disease, sex, age and complications ($P > 0.05$) (**Table 1**).

Table 1. General data of patients (Mean ± SD); [n (%)]

Classification	Control group (n=47)	Research group (n=50)	t/χ^2	*P*
Course of disease (d)	5.37 ± 2.62	5.44 ± 2.38	0.138	0.891
Sex			0.182	0.670
Male	31 (65.96)	35 (70.00)		
Female	16 (34.04)	15 (30.00)		
Age (years)	74.6 ± 3.44	75.8 ± 3.53	1.694	0.094
Diabetes			0.056	0.814
Yes	14 (29.79)	16 (32.00)		
No	33 (70.21)	34 (68.00)		
Hypertension			0.261	0.609
Yes	25 (53.19)	24 (48.00)		
No	22 (46.81)	26 (52.00)		
Coronary heart disease			0.017	0.896
Yes	21 (44.68)	23 (46.00)		
No	26 (55.32)	27 (54.00)		
Chronic obstructive pulmonary disease			0.091	0.763
Yes	23 (48.94)	26 (52.00)		
No	24 (51.06)	24 (48.00)		
Mechanical ventilation			0.046	0.831
Yes	31 (65.96)	34 (68.00)		
No	16 (34.04)	16 (32.00)		
Lying down postprandially for 2 h			0.182	0.670
Yes	16 (34.04)	15 (30.00)		
No	31 (65.96)	35 (70.00)		
Pneumonia severity index score	142.61 ± 15.45	143.22 ± 16.29	0.189	0.851
Acute physiology and chronic health evaluation II score	16.31 ± 5.12	16.94 ± 5.69	0.572	0.569
Procalcitonin	3.01 ± 1.27	3.17 ± 1.34	0.603	0.548

Table 2. Time of symptom disappearance (Mean ± SD)

Symptoms	Control group (n=47)	Research group (n=50)	χ^2	*P*
Fever clearance time (d)	4.05 ± 1.63	2.33 ± 1.16	6.016	< 0.001
Inflammation absorption time (d)	6.02 ± 1.52	5.13 ± 1.26	3.147	0.002
Cough disappearance time (d)	9.52 ± 1.26	7.59 ± 0.83	8.960	< 0.001

Time of symptom disappearance

Symptoms of patients with severe pneumonia were monitored. It turned out that patients in the research group presented earlier fever clearance, inflammatory absorption and cough disappearance than those in the control group ($P < 0.01$) (**Table 2**).

Changes in ABG indices before and after treatment

Changes in ABG indices ($PaCO_2$, PaO_2, pH) before and after treatment were observed with a blood gas analyzer. No significant changes were found between the control and study groups before treatment ($P > 0.05$). Whereas after treatment, $PaCO_2$ decreased ($P < 0.001$), PaO_2 and pH increased ($P < 0.01$) in both groups. The research group showed lower $PaCO_2$ ($P < 0.001$) and higher PaO_2 and pH ($P < 0.05$) than the control group (**Figure 1**).

Changes in PF parameters

PF parameters were tested both before and after treatment with a PF tester. Before treatment, there were no noticeable changes in

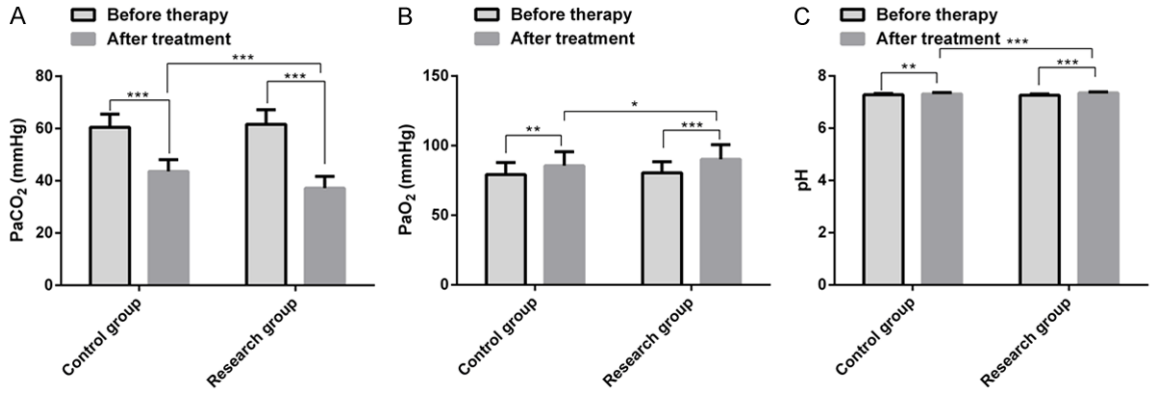

Figure 1. Changes in ABG indices. $PaCO_2$ decreases (A), and PaO_2 (B) and pH increase (C) in both study and control groups after treatment. $PaCO_2$ levels in the research group are significantly lower, while PaO_2 and pH levels are significantly higher, than those in the control group. Note: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

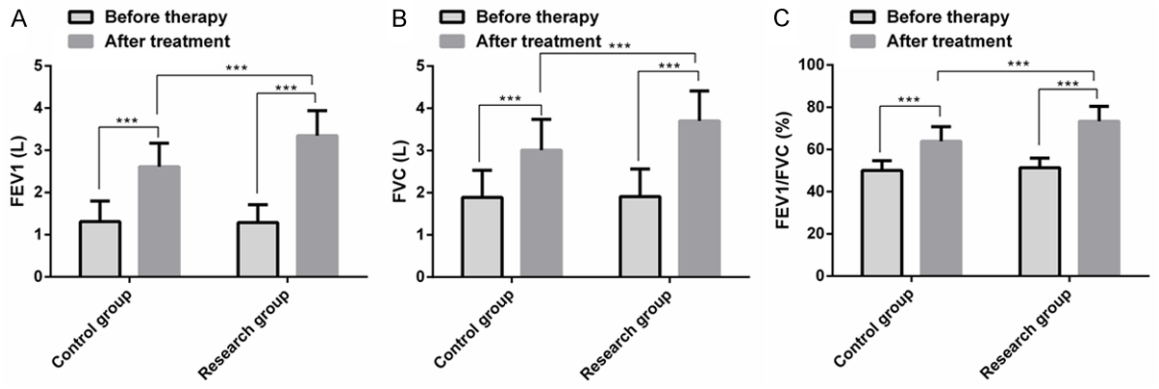

Figure 2. Changes in PF parameters. After treatment, FEV1 (A), FVC (B) and FEV1/FVC (C) increase significantly in the two groups, and in the research group are higher than those in the control group. Note: $^{***}P < 0.001$.

Table 3. Incidence of complications during treatment [n (%)]

Adverse reaction	Control group (n=47)	Research group (n=50)	χ^2	*P*
Nausea and vomiting	2 (4.26)	2 (4.00)	0.200	0.654
Skin rash	2 (4.26)	3 (6.00)	0.005	0.943
Diarrhea	1 (2.13)	3 (6.00)	0.200	0.654
Pruritus	2 (4.26)	1 (2.00)	0.003	0.957
Overall incidence rate	14.89	18.00	0.170	0.680

FEV1, FVC and FEV1/FVC between the two groups ($P > 0.05$). After treatment, those parameters showed increased levels in the two groups ($P < 0.001$), and in the research group they were higher than those in the control group ($P < 0.001$) (**Figure 2**).

Incidence of adverse reactions

Complications that occurring during treatment were observed. In the control group, 2 patients developed nausea and vomiting, 2 had rash, 1 had diarrhea, and 2 had pruritus, showing a incidence of adverse reactions of 14.89%; whereas in the research group, the incidence was 18.00% (2 patients with nausea and vomiting, 3 with rash, 3 with diarrhea, and 1 with pruritus). Therefore, there was no significant difference in incidence of adverse reactions between control group and research group ($P > 0.05$) (**Table 3**).

Comparison of clinical efficacy

The clinical efficacy in the two groups was assessed after 14 days of treatment. The overall response rate in the control group was 74.47% (cured, 10; markedly effective, 11; effective, 14; ineffective, 12), and that in the research group was 90.00% (cured, 24; mark-

Table 4. Comparison of clinical efficacy after 14 days of treatment [n (%)]

Clinical efficacy	Control group (n=47)	Research group (n=50)	χ^2	*P*
Cured	10 (21.28)	24 (48.00)	-	-
Markedly effective	11 (23.40)	13 (26.00)	-	-
Effective	14 (29.79)	8 (16.00)	-	-
Ineffective	12 (25.53)	5 (10.00)	-	-
Overall response rate	74.47	90.00	4.043	0.044

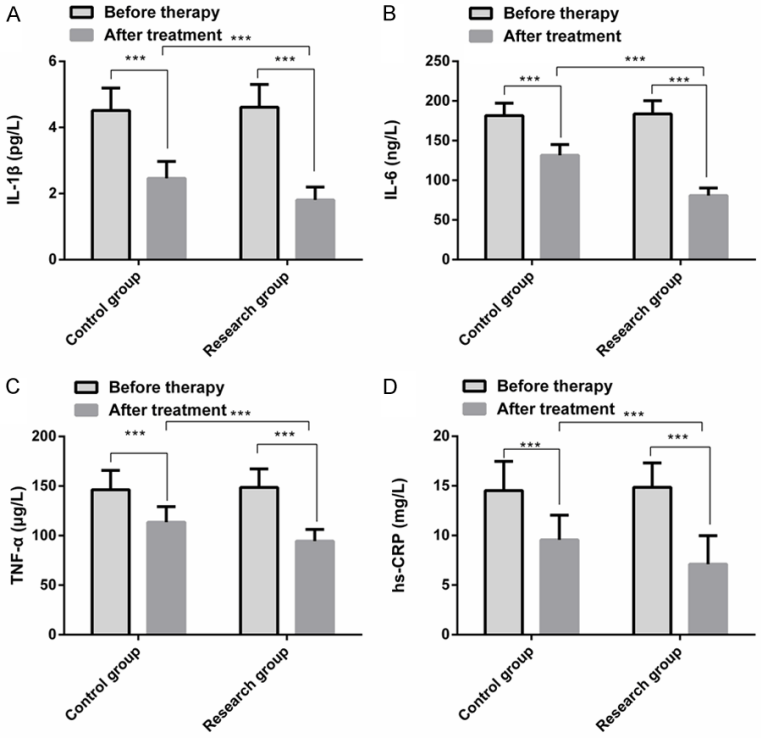

Figure 3. Changes in inflammatory cytokines. After treatment, serum levels of IL-1β (A), IL-6 (B), TNF-α (C) and hs-CRP (D) decrease in both group, and the decrease is greater in the research group. Note: ***$P < 0.001$.

edly effective, 13; effective, 8; ineffective, 5). The treatment in the research group produced a higher overall response rate than that in the control group ($P < 0.05$) (**Table 4**).

Changes in inflammatory cytokines

We also recorded the changes in inflammatory cytokines before and after treatment using ELISA. No significant differences were observed in serum levels of IL-1β, IL-6, TNF-α and hs-CRP between the two groups before treatment ($P > 0.05$). After treatment, those levels decreased in both groups ($P < 0.001$), and the decrease was greater in the research group ($P < 0.001$) (**Figure 3**).

Discussion

Characterized by acute onset and rapid progress, severe pneumonia in the elderly usually induces symptoms of high fever and respiratory dysfunction, as well as a series of complications [15]. In addition, shock, respiratory failure and other symptoms may occur in severe patients, resulting in great difficulties in treatment; thus, timely and effective interventions are essential [16].

UTI has been considered a good choice for the treatment of acute and chronic recurrent pancreatitis, and is an auxiliary drug for the rescue of acute circulatory failure. UTI is a non-antibacterial drug, so it needs to be combined with antibacterial drugs to achieve high efficacy [17, 18]. BIPM, an antibacterial drug, is effective in treating pneumonia, sepsis and other diseases caused by sensitive bacteria [19]. FEV1 and FVC are reliable indicators of PF impairments that decrease in patients with community-acquired pneumonia [20]. We developed a combination therapy of UTI and BIPM for acute treatment of severe pneumonia. It turned out that the PF in research group improved dramatically after treatment, greatly preventing respiratory failure of elderly patients. Moreover, the higher clinical efficacy and ABG indices in the research group indicated that the combination of these two drugs was highly effective against severe pneumonia in the elderly. Wang proposes that the overall efficacy of BIPM in lower respiratory tract infections or urinary tract infections reaches 94.70%; nevertheless, adverse reactions like skin rash and gastrointestinal upset are frequently reported [21]. Although some adverse reactions (such as nau-

sea, vomiting, rash) occurred during our treatment, there was no increase in incidence of adverse reactions observed in the research group.

Severe pneumonia in the elderly is manifested as an inflammatory cascade, and is associated with a massive release of inflammatory cytokines that triggers systemic inflammatory reaction [22]. In the report of Nakanishi, pretreatment with ULI reduces the release of inflammatory cytokines caused by coronary artery bypass grafting, which is related to the decrease in myocardial and lung injury following cardiopulmonary bypass [23]. Therefore, the combined use of ULI and BIPM in elderly patients with severe pneumonia may not only have antibacterial and anti-inflammatory effects, but also promote microcirculation and enhance organ function. Also, we found that ULI plus BIPM reduced the serum levels of IL-1β, IL-6, TNF-α and hs-CRP. They are widely considered as inflammatory cell biomarkers and pro-inflammatory cytokines responsible for increasing the production of other cytokines and aggravating impairments [24-26]. Similar to our findings, Zhang reports that ULI suppresses serum levels of CRP, IL-6 and TNF-α and alleviates inflammation in acute pancreatitis [27]. The reason may lie in the fact that the inhibitory effect of ULI on the production of inflammatory mediators prevents inflammatory cells from being over activated [28]. Intriguingly, BIPM has an antibacterial effect on anaerobic and aerobic bacteria [29]. Thus, the combined use of the two can avoid inflammation and bacteria-induced tissue damage, thereby reducing lung damage, and further effectively controlling the disease. Although we confirmed the high efficacy of UTI plus BIPM in the treatment of severe pneumonia in the elderly, there are still several deficiencies in the present study. First of all, the psychological state and quality of life of elderly patients after the combined treatment are not explored. Second, the anti-inflammatory mechanism of the two drugs in severe pneumonia remains unknown. These deficiencies will be addressed through more experiments.

Overall, the combination of UTI and BIPM shortens the time of symptom disappearance, enhances PF, and inhibits inflammation, achieving higher efficacy in the treatment of severe pneumonia in the elderly.

Disclosure of conflict of interest

None.

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