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Original Research Article

Effect of combined treatment with linezolid and ulinastatin on respiratory function and serum inflammatory factors in elderly patients with severe pneumonia

Zhengqiong He, Xi Wu*, Wei Zhang, Yan Li, Zhiyou Zeng, Yan Zhang, Guipeng Du

Intensive Care Unit, Nuclear Industry 416 Hospital. No. 4, North Fourth Section, Second Ring Road, Chenghua District, Chengdu City, China

For correspondence:* ***Email:* *wuxi19950126@126.com*

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Abstract

Purpose: *To investigate the clinical effect of linezolid in combination with ulinastatin on respiratory function and serum inflammatory factors in elderly patients with severe pneumonia.*
Methods: *Ninety-eight (98) elderly patients with severe pneumonia in Nuclear Industry 416 Hospital (January 2019 - January 2020) were equally randomized into group M and group N. Group M patients received linezolid alone, while those in group N received linezolid in combination with ulinastatin. Indices related to respiratory function such as maximal mid-expiratory flow (MMF), peak expiratory flow (PEF), maximal expiratory pressure (PE_{max}), maximal inspiratory pressure (Pi_{max}), as well as serum inflammatory factors such as C-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), were determined.*
Results: *Total treatment effectiveness, pulmonary function indexes and arterial blood gas indices were higher in group N, while serum inflammatory factors and CPIS and APACHE II scores were lower, when compared with group M ($p < 0.05$). The incidence of adverse reactions in both groups was comparable ($p > 0.05$).*
Conclusion: *Combined use of linezolid and ulinastatin produces marked therapeutic effect in elderly patients with severe pneumonia. It effectively lowers serum inflammatory factor levels, elevates arterial blood gas indices and improves pulmonary function. However, further clinical trials are required prior to its introduction in clinical practice.*

Keywords: *Severe pneumonia, Respiratory function, Serum inflammatory factor, Linezolid, Ulinastatin*

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INTRODUCTION

Severe pneumonia is a disease associated with high fatality rate, and it manifests mainly in circulatory failure and shock. Thus, it is also known as shock pneumonia. At onset, most patients with this disease present with cough, dyspnea, and clouding of consciousness [1-4]. Studies have shown that the mortality from severe pneumonia in China ranges from 6.2 to 34.6 %, mostly in the elderly population, especially in winter and spring [5-8]. Early

diagnosis and effective treatment are two important strategies for tackling severe pneumonia.

Previously, antibiotic therapy was the most common way to treat severe pneumonia. However, antibiotic treatment is hampered by the nagging problem of drug resistance. Several clinical studies have demonstrated that linezolid, an effective anti-inflammatory and anti-infective drug, is effective in the treatment of severe pneumonia, while ulinastatin restrains pro-inflammatory factors and mitigates multiple inflammatory responses [9-12]. In this study, 98 elderly patients with severe pneumonia were chosen as subjects for investigation of the clinical effect of combined use of linezolid and ulinastatin on the patients.

METHODS

General information

Ninety-eight (98) elderly patients with severe pneumonia in *Nuclear Industry 416 Hospital* (January 2019 - January 2020) were equally and randomly assigned to group M and group N. Group M comprised 28 males and 21 females, and their mean age and disease course were 73.4 ± 3.5 years and 6.3 ± 1.4 years. In group N patients, the male to female ratio was 27:22, and their mean age and mean disease course were 74.2 ± 3.6 years and 6.5 ± 1.6 years, respectively. No distinct differences in general information were found between the two groups (p > 0.05). This study obtained the approval of the Ethics Committee of Nuclear Industry 416 Hospital (approval no. 20181164), and followed the guidelines of Declaration of Helsinki as revised in 2013 [13]. The patients and their family members voluntarily signed informed consent.

Inclusion criteria

The patients included in this study were those who met the clinical diagnostic criteria for severe pneumonia in elderly patients based on the *Chinese Guidelines for Management of Community Acquired Pneumonia in Adults,* those aged 60 years and above, with length of hospital stay ≤ 2 weeks, and patients with complete medical records.

Exclusion criteria

Patients with drug allergy, those with other pulmonary diseases or systemic diseases, patients with mental disorders, and subjects who were uncooperative, were excluded from the study.

Treatments

All patients received routine treatment such as nutritional support, reduction of phlegm production, fluid infusion and oxygen inhalation, based on individual conditions. Both groups received intravenous infusion of 600 mg of linezolid (Pfizer Pharmaceuticals LLC; specification: 600-mg tablets; NMPA approval no. H20090516) in combination with 100 ml of physiological saline (0.9 % NaCl) for 1 - 2 h, twice a day [14,15].

Group N was additionally given extra 2 mL of ulinastatin injection (Guangdong Techpool Biochemical Pharmaceutical Co. Ltd.; specification: 2 mL; NMPA approval no. H20040506) dissolved in 500 mL of physiological saline (0.9 % NaCl) as intravenous infusion once-to-three times daily, each time lasting for 1 - 2 h. Both groups were treated for two weeks.

Table 1: General patient information

Parameter	Group M (n = 49)	Group N (n = 49)	t/χ^2	*P*-value
Age (years)	73.4±3.5	74.2±3.6	1.1153	0.2675
Disease course (years)	6.3±1.4	6.5±1.6	0.6585	0.5118
BMI (kg/m^2)	17.6±2.2	17.4±2.1	0.4603	0.6463
Smoking habit [n (%)]			0.3908	0.532
Yes	20 (40.82)	17 (34.69)		
No	29 (59.18)	32 (65.31)		
Drinking alcohol [n (%)]			0.1639	0.686
Yes	22 (44.90)	24 (48.98)		
No	27(55.10)	25 (51.02)		
Gender [n (%)]			0.0414	0.839
Male	28 (57.14)	27 (55.10)		
Female	21 (42.86)	22 (44.90)		
Residence [n (%)]			0.1922	0.661
Urban area	33 (67.35)	35 (71.43)		
Rural area	16 (32.65)	14 (28.57)		

Assessment of parameters/indices

Clinical efficacy

The treatment was deemed *markedly effective* if chest X-ray examination results showed evidence of cured lesions, disappearance of inflammation and absence of moist rales in the lungs. The treatment was deemed *effective* if the chest X-ray examination results showed reduced shadow and marked reduction in moist rales in the lungs. However, treatment was *ineffective* without improvement in patients' conditions, or with aggravated conditions. Total treatment effectiveness (TTE) was calculated as shown in Eq. 1:

$$TTE = \frac{(ME + E)}{T} \times 100 \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

where *TTE* = total treatment effectiveness; *ME* = markedly effective cases; *E* = effective cases, and *T* = all patients.

Pulmonary function

Pulmonary function indexes such as maximal mid-expiratory flow (MMF), peak expiratory flow (PEF), maximal expiratory pressure (PE_{max}) and maximal inspiratory pressure (Pi_{max}) of the patients after treatment were determined using a pulmonary function detector.

Serum levels of inflammatory factors

Fasting venous blood was extracted and centrifuged after clotting. Then, the serum samples were subjected to determination of levels of C-reactive protein (CRP), procalcitonin (PCT), and tumor necrosis factor-α (TNF-α) using radioimmunoassay, chemiluminescence enzyme immunoassay, and enzyme-linked immunosorbent assay (ELISA), respectively.

Arterial blood gas indices

Arterial partial pressure of oxygen (PaO_2) and fraction of inspired oxygen (FiO_2) of the patients were determined with a blood-gas analyzer. Thereafter, the oxygenation index (OI) was calculated using the formula shown in Eq 2.

$$OI = \frac{PaO_2}{FiO_2} \quad \ldots\ldots\ldots\ldots\ldots\ldots (2)$$

CPIS and APACHE II scores

Pulmonary infection in patients was evaluated using clinical pulmonary infection score (CPIS) covering body temperature, tracheal secretions, white blood cell count, X-chest radiograph, oxygenation, pulmonary infiltration and culture results for tracheal aspirates. The total score was 12 points, and higher scores indicated more severe infections. Acute physiology and chronic health evaluation (APACHE II) comprised three parts: age, acute physiology and chronic health status. A higher APACHE II score denoted more severe disease.

Incidence of adverse reactions

The adverse reactions to medication of both groups during treatment were recorded.

Statistical analysis

The data were processed by SPSS 20.0, while GraphPad Prism 7 (GraphPad Software, San Diego, USA) was for drawing data graphs. Measurement data are shown as mean ± standard deviation (SD), and tested with *t*-test, while enumeration data are presented as numbers and percentages (n (%)), and tested using χ^2 test and normality test. Differences were assumed statistically significant at $p < 0.05$.

RESULTS

Clinical efficacy

Table 2 demonstrated lower total treatment effectiveness in group M than in group N ($p < 0.05$).

Pulmonary function

The post-treatment pulmonary function indexes, i.e., MMF, PEF, PE_{max} and Pi_{max} were markedly higher in group N than in group M ($p < 0.001$). See Table 3.

Table 2: Comparison of clinical efficacy

Group	Ineffective cases	Effective cases	Markedly effective cases	Total effectiveness
M (n = 49)	13 (26.53)	19 (38.78)	17 (34.69)	36 (73.47)
N (n = 49)	5 (10.20)	18 (36.74)	26 (53.06)	44 (89.80)
χ^2				4.3556
P-value				0.037

Table 3: Comparison of levels of pulmonary function indices

Group	MMF (L/s)	PEF (L/s)	PE_{max} (%)	Pi_{max} (%)
M (n = 49)	1.06±0.13	1.36±0.18	38.13±4.64	72.81±6.32
N (n = 49)	1.62±0.18	2.03±0.26	46.71±5.15	82.82±7.11
t	17.6548	14.8311	8.6642	7.3658
P-value	0.000	0.000	0.000	0.000

Table 4: Comparison of serum inflammatory factors

Group	CRP (mg/L)	PCT (ng/L)	IL-6 (ng/L)	TNF - α (pg/L)
M (n = 49)	22.17±6.82	1.99±0.54	47.07±8.83	40.62±8.55
N (n = 49)	15.43±5.13	1.24±0.42	40.24±8.79	32.17±7.47
t	5.5285	7.6743	3.8373	5.2098
P-value	0.000	0.000	0.0002	0.000

Serum inflammatory factors

After treatment, the levels of serum inflammatory factors i.e., CRP, PCT, IL-6 and TNF - α were lower in group N than in group M ($p < 0.05$; Table 4).

Arterial blood gas indices

The post-treatment levels of arterial blood gas indexes (PaO_2 and OI) were significantly higher in group N than in group M ($p < 0.001$). The data are presented in Figure 1.

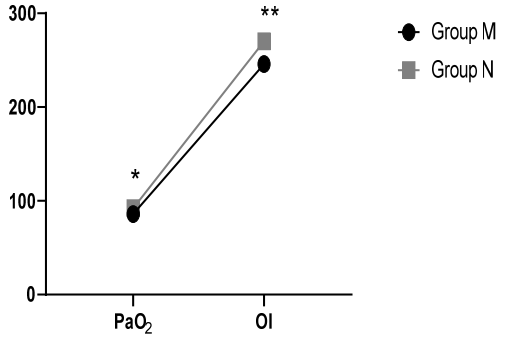

Figure 1: Comparison of levels of arterial blood gas indexes. *$P < 0.001$, PaO_2 value in group M vs PaO_2 value in group N; **$p < 0.001$, OI value in group M vs OI value in group N

CPIS and APACHE II scores

As shown in Figure 2, the CPIS and APACHE II scores in group M were higher than the corresponding scores in group N ($p < 0.001$).

Incidence of adverse reactions

Figure 3 and Figure 4 showed no distinct differences in the overall incidence of adverse reactions between the two groups ($p > 0.05$).

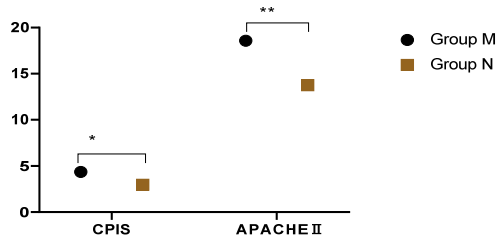

Figure 2: Comparison of CPIS and APACHE II scores. *$P < 0.001$, CPIS score in group N vs CPIS score in group M; *$p < 0.001$, APACHE II score in group N vs APACHE II score in group M

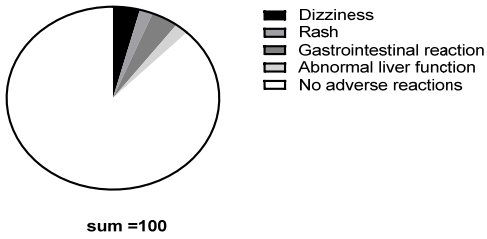

Figure 3: Adverse reactions in group M. This group had 2 patients with dizziness (4.08 %), 1 patient with rash (2.04 %), 2 patients with gastrointestinal reaction (4.08 %), and 1 patient with abnormal liver function (2.04 %). The overall incidence was 12.24 %

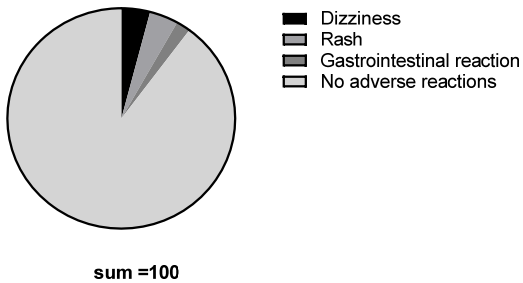

Figure 4: Adverse reactions in group N. This group had 2 patients with dizziness (4.08 %), 2 patients with rash (4.08 %), and 1 patient with gastrointestinal reaction (4.08 %). No patient had abnormal liver function. There was 10.20 % overall incidence in this group

DISCUSSION

Nowadays, important ways used in treating severe pneumonia in elderly patients in clinics involves inhibition of the growth and multiplication of pathogenic bacteria so as to establish long-term and effective immune response. Linezolid, a broad-spectrum antibiotic for gram-positive cocci, destroys the enzymes used for the synthesis of pathogenic bacterial proteins and blocks the binding of DNA and RNA to ribosomes in pathogenic bacterial cells, thereby inhibiting bacterial multiplication [16,17].

Ulinastatin is a broad-spectrum protease inhibitor that regulates the permeability and stability of lysosomal membranes by limiting the release of lysosomal enzyme, and accelerating protein metabolism. Besides, this drug blocks the multi-target response in inflammation, scavenges inflammatory transmitters and oxygen radicals, and restores immune function of leukocytes in humans [18]. The two drugs exert very significant anti-inflammatory and anti-infection effects, but not much was hitherto known about the safety and clinical efficacy of their combined use. Based on that, the study investigated the effects of linezolid combined with ulinastatin.

The results obtained showed that after treatment, total effectiveness and levels of pulmonary function indexes (MMF, PEF, PE_{max} and Pi_{max}), and arterial blood gas indices (PaO_2 and OI) in group M were lower. However, the serum inflammatory factor levels (CRP, PCT, IL-6 and TNF-α) as well as CPIS and APACHE II scores were lower in group N, with similar incidence of adverse reactions in both groups.

Therefore, linezolid in combination with ulinastatin significantly improved ventilatory function, elevated lung capacity, reduced serum inflammatory factor levels, and inhibited inflammatory response, with significant efficacy and high safety. These results are similar to those presented in a previous study showing that the combined application of ulinastatin and linezolid produced marked therapeutic effect in patients with severe pneumonia through boosting of cellular immune response, inhibition of release of inflammatory mediators, up-regulation of synthesis of immunoreactive proteins, and enhancement of pulmonary function [19].

CONCLUSION

The combined use of linezolid and ulinastatin produces marked therapeutic effect in elderly patients with severe pneumonia, effectively lowers serum levels of inflammatory factors, elevates arterial blood gas indices, and improves pulmonary function. However, further clinical trials are required prior to its introduction in clinical practice.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Zhengqiong He and Xi Wu conceived and designed the study, and drafted the manuscript. Zhengqiong He, Wei Zhang, Yan Li, Zhiyou Zeng, Yan Zhang, and Guipeng Du collected, analyzed and interpreted the experimental data. Xi Wu, Wei Zhang and Yan Li revised the manuscript for important intellectual contents. All authors read and approved the final manuscript.

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