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

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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-a (TNF-a), 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

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) | χ² | 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/m²)              | 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:

\[
TTE = \frac{(ME + E) \times 100}{T}
\]  

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\(_{\text{max}}\)) and maximal inspiratory pressure (Pi\(_{\text{max}}\)) 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-\(\alpha\) (TNF-\(\alpha\)) 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.

\[
OI = \frac{PaO_2}{FiO_2}
\]

**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 \(\chi^2\) 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\(_{\text{max}}\) and Pi\(_{\text{max}}\) were markedly higher in group N than in group M (\(p < 0.001\)). See Table 3.

| 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) |
| \(\chi^2\) | 4.3556 | | | |
| \(P\)-value | 0.037 | | | |

Table 2: Comparison of clinical efficacy.

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Table 3: Comparison of levels of pulmonary function indices

| Group | MMF (L/s) | PEF (L/s) | PEmax (%) | Plmax (%) |
|-------|-----------|-----------|------------|------------|
| 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 (PaO2 and OI) were significantly higher in group N than in group M (*p < 0.001). The data are presented in Figure 1.

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

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).
**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, $P_{E_{\text{max}}}$ and $P_{I_{\text{max}}}$), and arterial blood gas indices ($P_{\text{aO}_2}$ and $O_{1}$) in group M were lower. However, the serum inflammatory factor levels (CRP, PCT, IL-6 and $\text{TNF-\alpha}$) 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.

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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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REFERENCES

1. De Rosa M, Zanfardino A, Notomista E, Wichelhaus TA, Saturnino C, Varcamonti M, Sorente A. Novel promising linezolid analogues: rational design, synthesis and biological evaluation. Eur J Med Chem 2013; 69: 779-785.

2. Kjöllerström P, Brito MJ, Gouveia C, Ferreira G, Varandas L. Linezolid in the treatment of multidrug-resistant/extensively drug-resistant tuberculosis in paediatric patients: experience of a paediatric infectious disease unit. Scand J Infect Dis 2011; 43(6-7): 556-559.

3. Decousser JW, Desroches M, Bourgeois-Nicolaos N, Potier J, Jehl F, Lina G, Cattoir V, Vandenesh F, Doucel-Populaire F. Microbs Study Group. Susceptibility trends including emergence of linezolid resistance among coagulase-negative staphylococci and meticillin-resistant Staphylococcus aureus from invasive infections. Int J Antimicrob Agents 2015; 46(6): 622-630.

4. Chuang YC, Lin HY, Chen PY, Lin CY, Wang JT, Chang SC. Daptomycin versus linezolid for the treatment of vancomycin-resistant enterococcal bacteraemia: implications of daptomycin dose. Clin Microbiol Infect 2016; 22(10): 890.e1-890.e7.

5. Ozkaya-Parlakay A, Kara A, Celik M, Ozsurekci Y, Karadag Oncel E, Ceyhan M, Cengiz AB. Early lactic acidosis associated with linezolid therapy in paediatric patients. Int J Antimicrob Agents 2014; 44(4): 334-336.

6. Wang Y, Zou Y, Xie J, Wang T, Zheng X, He H, Dong W, Xing J, Dong Y. Linezolid versus vancomycin for the treatment of suspected methicillin-resistant Staphylococcus aureus nosocomial pneumonia: a systematic review employing meta-analysis. Eur J Clin Pharmacol 2015; 71(1): 107-115.

7. Barco S, Bandettini R, Maffia A, Tripodi G, Castagnola E, Cangemi G. Quantification of piperacillin, tazobactam, meropenem, ceftazidime, and linezolid in human plasma by liquid chromatography/tandem mass spectrometry. J Chemther 2015; 27(6): 343-347.

8. Guo H, Jiang C, Sun X. Therapeutic effects and mechanism of salbutamol combined with ulinastatin on treating paraquat poisoning. Cell Biochem Biophys 2014; 70(3): 1559-1563.

9. Sui B, Li Y, Ma L. Postconditioning improvement effects of ulinastatin on brain injury following cardiopulmonary resuscitation. Exp Ther Med 2014; 8(4): 1301-1307.

10. Jiang XM, Hu JH, Wang LL, Ma C, Wang X, Liu XL. Ulinastatin alleviates neurological deficiencies evoked by transient cerebral ischemia via improving autophagy, Nrf-2-ARE and apoptosis signals in hippocampus. Physiol Res 2018; 67(4): 637-646.

11. Chen X, Wang Y, Luo H, Luo Z, Liu L, Xu W, Zhang T, Yang N, Long X, Zhu N, et al. Ulinastatin reduces urinary sepsis-related inflammation by upregulating IL-10 and downregulating TNF-α levels. Mol Med Rep 2013; 8(1): 29-34.

12. Yang B, Gao M, Wang K, Jiang Y, Peng Y, Zhang H, Yang M, Xiao X. Intraintestinal administration of ulinastatin protects against sepsis by relieving intestinal damage. J Surg Res 2017; 211: 70-78.

13. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013; 310(20): 2191-2194.

14. Wang Z, Zhuang X, Wei R, Wang C, Xue X, Mao L. Protective effects of Acanthopanax vs. Ulinastatin against severe acute pancreatitis-induced brain injury in rats. Int Immunopharmacol 2015; 24(2): 285-298.

15. Wang KY, Yang QY, Tang P, Li HX, Zhao HW, Ren XB. Effects of ulinastatin on early postoperative cognitive function after one-lung ventilation surgery in elderly patients receiving neoadjuvant chemotherapy. Metab Brain Dis 2017; 32(2): 427-435.

16. Li C, Ma D, Chen M, Zhang L, Zhang L, Zhang J, Qu X, Wang C. Ulinastatin attenuates LPS-induced human endothelial cells oxidative damage through suppressing JNK/c-Jun signaling pathway. Biochem Biophys Res Commun 2016; 474(3): 572-578.

17. Feng M, Shu Y, Yang Y, Zheng X, Li R, Wang Y, Dai Y, Qiu W, Lu Z, Hu X. Ulinastatin attenuates experimental autoimmune encephalomyelitis by enhancing anti-inflammatory responses. Neurochem Int 2014; 64: 64-72.

18. Qin ZS, Tian P, Wu X, Yu HM, Guo N. Effects of ulinastatin administered at different time points on the pathological morphologies of the lung tissues of rats with hyperthermia. Exp Ther Med 2014; 7(6): 1625-1630.

19. Karino F, Deguchi N, Kanda H, Ohe M, Kondo K, Tada M, Kuraki T, Nishimura N, Moriyama H, Ikawa K, et al. Evaluation of the efficacy and safety of biapenem against pneumonia in the elderly and a study on its pharmacokinetics. J Infect Chemother 2013; 19(1): 98-102.