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Short Communication

Clinical Study on Ulinastatin Combined with Ambroxol in the Treatment of AECOPD Complicated with Type II Respiratory Failure

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ABSTRACT

The Objective of the present study was to observe and analyze the efficacy of ulinastatin combined with ambroxol in the treatment of AECOPD complicated with type II respiratory failure. A total of 180 patients treated in our hospital due to AECOPD complicated with type II respiratory failure were enrolled in the study and divided into study group and reference group, each with 90 patients. The study group was treated with ulinastatin and ambroxol, while general routine treatment was implemented in the reference group. The treatment outcomes were compared between the two groups. The blood content levels of WBC, CRP and PCT were compared between the two groups after one week of treatment. The results showed that the improvement effect was significantly superior in the study group, $p<0.05$. The arterial blood gas analysis showed that the arterial blood PO_2 was elevated and PCO_2 was decreased in the study group. The difference was statistically significant ($P<0.05$). It was concluded that the application of ulinastatin combined with ambroxol in the treatment of AECOPD complicated with type II respiratory failure can significantly improve the treatment effect, help patients actively improve the condition and promote body recovery as soon as possible.

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Authors' Contribution
XL enrolled and grouped patients. XL and XZ designed the treatment plan. XZ and XS treated different groups. XL and XS processed data for comparative analysis. XL wrote the manuscript.

Key words
Ulinastatin, Ambroxol, Combination therapy, AECOPD complicated with type II respiratory failure, Therapeutic effect

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease characterized by persistent airflow limitation. The pathogenesis is closely related to long-term inhalation of harmful tobacco smoke or particles-induced inflammatory reactions (Wendong *et al*., 2018; Shaotian *et al*., 2016; Yan *et al*., 2018). The lung function of COPD patients shows different degrees of progressive hypofunction. In the case of continuous disease progression, it will seriously affect the patient's labor ability and quality of life, bringing great economic burden to the family and society.

Inflammatory response is one of the important pathogenesis of COPD. Due to the release of extensive inflammatory mediators in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD), systemic inflammatory response syndrome (SIRS) is often induced, easily leading to persistent damage to respiratory function and damage to multiple organs outside the lung. Hence, anti-inflammation is one of the essential treatments for AECOPD (Hongtao *et al*., 2017; Peter, 2017). Ulinastatin is a protease inhibitor extracted from the fresh urine of healthy people. Ambroxol is a commonly used expectorant effective in the treatment of patients with AECOPD complicated with type II respiratory failure (Jing *et al*., 2020). The combination of the two has been widely used. This study investigates the clinical effects of ulinastatin combined with ambroxol in the treatment of AECOPD complicated with type II respiratory failure.

Materials and methods

The study included 180 patients treated in our hospital from August 2016 to June 2019 due to AECOPD complicated with type II respiratory failure. The inclusion and exclusion criteria were those meeting the Chinese expert diagnosis and treatment guidelines for AECOPD developed in 2017, as shown in Figure 1; those supporting COPD diagnosis based on physical examination and chest X-ray examination, medical history inquiry; those with aggravated shortness of breath recently, showing increased wheezing, cough, chest tightness, etc. in clinical symptoms; those with changes in sputum color, expectoration volume, viscosity of sputum, etc.; arterial blood gas analysis supports the diagnosis for type II respiratory failure; those without combined pneumothorax, pleural effusion,

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hemoptysis or recent thoracic and abdominal surgery; those with no serious heart, brain, kidney disease; those with no severe infection, tuberculosis, bronchial asthma, lung cancer and other respiratory diseases in other parts. Patients were randomly divided into study group (90 cases) and reference group (90 cases). The patients in the study group had an average age of 66.8 ± 3.2 years with 48 males and 42 females; the patients in the reference group had an average age of 67.3 ± 3.6 years, with 46 males and 44 females. Comparison of the data of the two groups shows comparability (P>0.05).

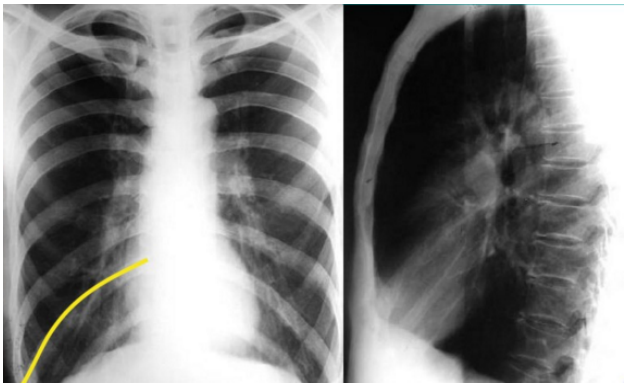

Fig. 1. Patient's imaging examination chart.

The study group was given conventional treatment program. That is, the main contents included nutritional support, oxygen inhalation, correction of fluid and electrolyte imbalance, bronchiectasis, use of antibiotics, spasmolysis and asthma relief, atomization and aspiration of sputum. On this basis, the study group was given combination therapy of ulinastatin and ambroxol. That is: 30 mg ambroxol hydrochloride (produced by Shenyang Xinma Pharmaceutical Co., Ltd.) was added to 100 ml 0.9% sodium chloride injection to be used three times a day; 100,000 U ulinastatin injections (produced by Guangdong Tianpu Biochemical Pharmaceutical Co., Ltd.) was added with 100ml 0.9% sodium chloride injection for intravenous injection three times a day.

Ambroxol hydrochloride, with molecular formula C13H18Br2N2O•HCl, is white to slightly yellow crystalline powder, which is almost odorless. It promotes the elimination of sticky secretions inside the respiratory tract and reduces the retention of mucus, thus significantly promoting expectoration. It is suitable for acute and chronic respiratory diseases with abnormal sputum secretion and expectoration dysfunction. This product can promote mucus elimination and secretion dissolution, which can promote the elimination of sticky secretions in the respiratory tract and reduce the retention of mucus, thus significantly promoting expectoration and improving respiratory status (Soo *et al*., 2018). After treatment with this product, mucus secretion from the patient can be restored to normal conditions. Cough and expectoration amount will usually be significantly reduced, so that the surface active material on the mucous membranes of the respiratory tract can perform its normal protective function. The half-life period is 7-12 h, no accumulation will be found as it is mainly metabolized by the liver, and 90% is cleared by the kidneys. The main ingredient of ulinastatin injection is ulinastatin, a glycoprotein extracted from fresh human urine that inhibits the activity of various proteolytic enzymes. It serves as a rescue adjuvant for acute pancreatitis, chronic recurrent pancreatitis and acute circulatory failure. The glycoprotein extracted and purified from human urine is a protease inhibitor, which can inhibit activity of various pancreatins such as trypsin. In addition, this product can stabilize lysosomal membrane, inhibit the release of lysosomal enzymes, inhibit the production of myocardial inhibitors, which can thus be used in the rescue treatment of acute circulatory failure (Chaogui *et al*., 2015). In the case of intravenous injection of 300,000 units /10 ml in healthy normal male, blood concentration will decrease linearly within 3 h, and the elimination half-life time is 40 min; 6 h after the administration, 24% dosage will be discharged from the urine.

The blood gas analysis indicators were observed before and after treatment. That is, the patient's pH, PO_2, PCO_2 test results were recorded. Recording of acute physiology and chronic health evaluation (APACHE II) score and statistics of the level of inflammatory markers were made.

The data were processed by SPSS21.0 statistical analysis software. The measurement data and the count data were expressed by means of mean ± average ($\bar{x}$±s), natural number (n) and percentage (%), respectively, and t and X^2 were compared. Statistical value exists when $p < 0.05$.

Results

Table I shows the comparison of inflammatory indicators between the study and reference groups. After one week of treatment, the improvement of the indicators is more advantageous in the study group, p<0.05.

Table II shows the cmparison of blood gas parameters between the two groups. The study group has superior improvement in blood gas index after one week of treatment, p<0.05.

Table III shows comparison of APACHE II scores after treatment. APACHE II score is significantly lower in the study group, $p < 0.05$.

Table I. Comparison of inflammatory indicators in the treatment between the two groups ($\bar{x}$±s).

Group	CRP (mg/L)		PCT (ng/ml)		WBC (10^9/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Reference group	53.40±12.17	13.22±2.10	1.60±0.13	0.49±0.08	13.38±2.11	6.31±0.59
Study group	55.37±10.93	4.85±1.36	1.59±0.16	0.10±0.05	13.90±2.16	8.35±0.58
t	0.40	7.69	0.03	10.26	0.82	13.21
p	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

CPR, C reactive protein; PCT, p rocalcitonin;WBC, white blood cells.

Table II. Comparison of blood gas parameters between the two groups ($\bar{x}$ ±s).

Indicator	Time	Study group	Reference group
PO_2(mm/Hg)	Before treatment	52.4±5.5	51.9±5.2
	One week after treatment	87.9±3.0	74.2±3.8
PCO_2(mm/Hg)	Before treatment	74.7±7.2	75.6±8.0
	One week after treatment	38.4±2.5	49.7±2.2
PaO_2/FiO_2 (mmHg)	Before treatment	146.9±12.3	147.8±16.8
	One week after treatment	147.8±16.8	208.6±10.7
pH	Before treatment	7.30±0.09	7.29±0.06
	One week after treatment	7.43±0.08	7.40±0.05

PO_2, partial pressure of Oxygen; PCO_2, partial pressure of corban dioxide; PaO_2/FiO_2, ratio of arterial oxygen partial pressure to fractional inspired oxygen.

Table III. Comparison of APACHE II scores after treatment in the two groups ($\bar{x}$ ±s).

Group	APACHE II score before treatment (point)	APACHE II score after treatment (point)
Study group	19.03±2.10	15.40±3.20
Reference group	18.97±2.35	9.07±1.27
t	1.20	9.88
p	>0.05	<0.05

Discussion

COPD is a chronic airway inflammatory disease caused by many factors, which seriously endangers people's health in our country. According to relevant epidemiological survey results, the total incidence of COPD in China is 9.11%-12%, and the disease features easily repeated episodes and a higher mortality rate. Moreover, acute exacerbation of COPD, especially AECOPD complicated with type II respiratory failure, poses a direct threat to the patients' safety, which is one of the key factors leading to COPD death (Wancang *et al*., 2018; Yanhong *et al*., 2017). It is especially essential to adopt scientific and effective drug therapy to maintain patients' health.

Ulinastatin, a glycoprotein found in the urine of healthy people, can effectively inhibit activity of various proteases such as fibrinoclase, trypsin and α-chymotrypsin. Ulinastatin also antagonizes a variety of inflammatory factor, which not only stabilizes lysosome membrane, but also inhibits lysosome release (Yanhong *et al*., 2017). In addition, ulinastatin can also remove oxygen free radicals in tissues and circulation, improve the microcirculatory function state of the body during shock, and alleviate the damage in vital organs of the body caused by ischemia-reperfusion, thus playing an important role in protecting important organs in the body such as kidney, lung and liver.

Acute exacerbation of COPD will be caused if sputum is not effectively discharged from the lungs of COPD patients. Ambroxol is a commonly used expectorant in the clinic. It can act on airway endocrine cells, regulate the liquid secretion function of secretory cells, promote the production of PS and enhance the motor function of trachea cilia, promote the excretion of sputum, improve lung ventilation and pulmonary gas exchange and diffuse function (Susan *et al*., 2015; Egro *et al*., 2015; Susan

et al., 2016). Therefore, in this study, AECOPD patients were treated with ulinastatin to inhibit the synthesis and release of inflammatory mediators. Meanwhile, ambroxol was combined to scavenge oxygen free radicals, fight against inflammation and promote sputum excretion. The therapeutic effect of ulinastatin combined with ambroxol in the treatment of AECOPD complicated with respiratory failure was observed.

The study results showed that in comparison of blood levels of WBC, CRP and PCT between the two groups after one week of treatment, the study group had significantly better improvement effect than the reference group, $p<0.05$; arterial blood gas analysis showed that the arterial blood PO_2 of the study group increased while PCO_2 decreased, and the difference was statistically significant ($p<0.05$). This is consistent with the relevant research results.

Conclusion

In summary, in the treatment of patients with AECOPD complicated with type II respiratory failure, the key is to actively correct hypoxia, control recurrent COPD attacks, relieve clinical symptoms and reduce complications. To achieve the above therapeutic effects, systemic treatment must be carried out for the pathogenesis of chronic obstructive pulmonary disease. In view that the pathological mechanism of chronic obstructive pulmonary disease is inflammatory reaction and oxygen free radical production, ulinastatin and ammonia are added on the basis of conventional treatment, namely anti-inflammation, asthma relief, atomization, nutritional support and mechanical ventilation. Ulinastatin combined with ambroxol can achieve good results in the treatment of AECOPD complicated with type II respiratory failure, and the effect is superior to that of conventional treatment alone.

Limitations

However, there are few cases in this study, and the effect of bacterial infection and non-bacterial infection on the treatment effect is not distinguished. In future, the infection categories can be grouped to further explain the therapeutic effect of ulinastatin combined with ambroxol.

Statement of conflict of interest

The declare there is no conflict of interest.

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