

Study on effect of Combivent combined with glucocorticoids in the treatment of patients with AECOPD

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Abstract: We observed the effect of Combivent combined with glucocorticoids in the treatment of patients with AECOPD to explore a better drug treatment for AECOPD. The clinical observation of two clinical curative effective was carried out. Firstly, 100 patients were equally divided into treatment group and control group, who were given basic treatment. The control group was treated with inhalation of salbutamol sulfate and the other was with inhalation of Combivent and glucocorticoid. The clinical effect, dyspnea score, PaO₂, PaCO₂ and pulmonary function index were observed and compared. The second, 100 patients with AECOPD were divided into the conventional group, the short range group and the long range group, all of that were treated with inhalation of Combivent. The short and the long were treated with glucocorticoid for 7d and 15d. Pulmonary function index was monitored at sixth and fifteenth days after treatment. The incidence of AECOPD was compared with the incidence of complication. Firstly, after 10 days of treatment, the treatment group's total efficiency, dyspnea score, PaO₂, PaCO₂, were significantly better than the control group and the treatment in the two groups after the above indexes were significant better than those before treatment. The differences were statistically significant (P<0.05). The second time, the short and the long's VC, FVC, FEV₁ were higher than the conventional, the recurrence rate was decreased, the incidence of complications in the short was significantly lower than that in the long and the difference was statistically significant (P<0.05). The effect of Combivent combined with glucocorticoid was exactly and the short's complication was low, which is worth to be popularized.

Keywords: Glucocorticoid, Combivent, ipratropium bromide, effect, AECOPD.

INTRODUCTION

In recent years, the incidence and mortality of chronic obstructive pulmonary disease (COPD) were increasing. COPD (LEE *et al.*, 2012) was a serious hazard to human health as a common disease and frequently occurring disease, which seriously affected the patient's quality of life, and the mortality rate was not only high, but also it brought heavy economic burden to patients and their families and the society. Acute exacerbation of chronic obstructive pulmonary disease was an acute onset process, and the symptoms of respiratory system in COPD patients were acute exacerbation. Typical symptoms had dyspnea, cough, sputum volume or sputum that was purulent, beyond the daily variation and it needed to change the drug treatment. The World Health Organization data showed that COPD world disease burden will rise from twelfth in 1990 to fifth in 2020, global death will be from 1990 sixth to third place. The acute exacerbation of COPD in patients with 0.5~3.5 occurred annually (Marchetti *et al.*, 2012). AECOPD (Hollander *et al.*, 2015) had become a common disease and frequently occurring disease in hospital emergency work at all levels. This paper would introduce the research progress of AECOPD from the etiology, mechanism, treatment target, and drugs of AECOPD, again through clinical observation

of two Combivents combined with glucocorticoids in the treatment of AECOPD and study the AECOPD for better drug regimens.

Etiology and pathogenesis of AECOPD

The causes of AECOPD included bronchial pulmonary infection, air pollution, heart failure, etc. Among them, the infection was different, and the different regions, the populations and the seasonal pathogenic bacteria were different, but also the diagnosis and treatment methods (fig. 1). The role of viruses and atypical pathogens in AECOPD had gradually been emphasized. Currently thinking, the pathogenesis of AECOPD was related to the oxidative stress, the protease and the imbalance of the protease, the protease and the inflammation of the lung that caused by the inhalation of harmful particles or gases. Inflammation cells in lungs was activated after release of leukotriene B₄, IL-8, tumor necrosis factor and other inflammatory mediators, which lead to mucous cells and goblet cell metaplasia, proliferation, mucus secretion, pulmonary fibrosis and structural damage of lung tissue. Abnormal distribution of cholinergic receptors also played an important role. In addition, the incidence of COPD had some relationship with the severity of disease itself, and the average incidence of AECOPD II patients is 2.68%; the incidence of GOLD grade COPD was 3.43%;

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the incidence of patients with pulmonary function was significantly increased. At the same time, the study also found that the incidence rate of the disease was higher and the incidence of the disease was higher (Tang *et al.*, 2010). And AECOPD also had a high mortality (fig. 2).

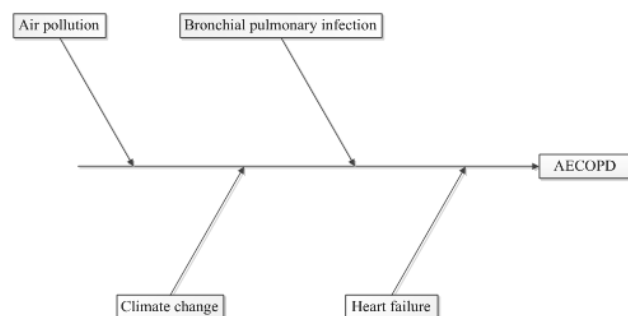


Fig. 1: The cause of AECOPD factor

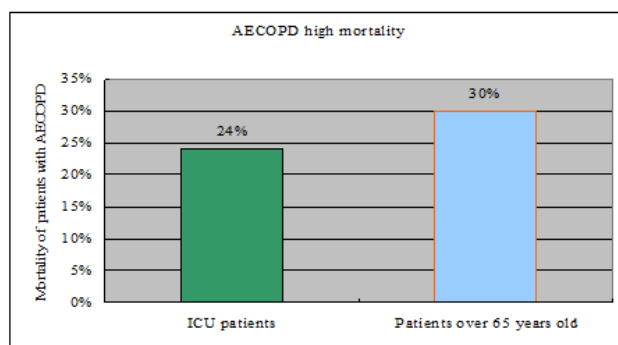


Fig. 2: The mortality of AECOPD in China by 2010

The diagnosis of AECOPD

After inhalation of bronchial dilation agent FVC/FEV₁ is less than seventy percent, which can clearly prove the existence of persistent airflow limitation, except for other diseases, then the diagnosis can be diagnosed as COPD. While AECOPD diagnosis and treatment of Chinese expert (Jiang *et al.*, 2012) consensus (2014 Revision) stressed: "AECOPD can't be proved except for clinical diagnosis". And it was pointed out that so far, no single biomarkers can be applied to the clinical diagnosis and evaluation of AECOPD". Diagnosis depends on clinical and laboratory examination to exclude acute dyspnea, cough and expectoration of sudden changes in the other specific diseases, in order to determine the acute exacerbation of chronic obstructive pulmonary disease (AECOPD). AECOPD was a kind of acute onset, chronic obstructive pulmonary disease (COPD) patients whose symptoms of respiratory system were acute exacerbation, beyond the daily variability, which lead to the need for changes in drug treatment. AECOPD can't be proved except for clinical diagnosis, clinical and laboratory tests have not found other specific diseases (e.g. pneumonia, congestive heart failure, pneumothorax, pleural effusion, pulmonary embolism and arrhythmia, etc.). The patients with exacerbation were often difficult to complete the pulmonary function test. FEV₁ may suggest a severe

attack if it is less than one liter. The arterial blood gas analysis was PaO₂ < 60mmHg and SaO₂ < 90%, which suggests respiratory failure under the condition of the respiratory air at the sea level. Such as PaO₂ < 50 mmHg, PaCO₂ > 70 mmHg, pH < 7.30 is prompt critical condition, which needs for intensive care or in ICU noninvasive or invasive mechanical ventilation (You, 2011). And chest X-ray imaging can help COPD aggravate the disease with other similar symptoms. And the number of red blood cell and the red blood cell pressure reflect situation of the red blood cell or the bleeding.

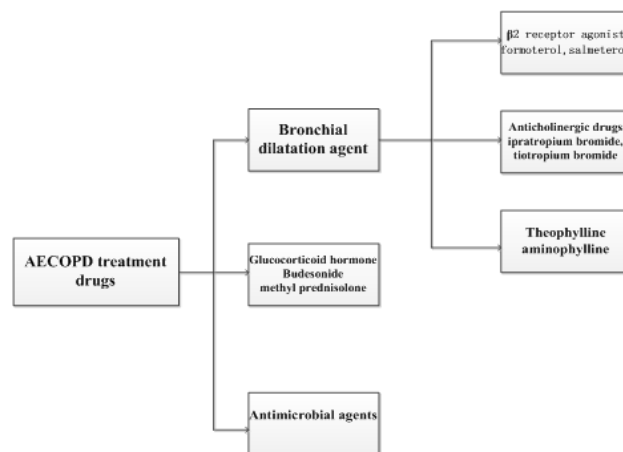


Fig. 3: AECOPD classification of drugs

AECOPD targets

The treatment of AECOPD target included two aspects. Firstly, it's to relieve symptoms quickly, reduce clinical manifestations, and the ease of patients with acute exacerbation of degree; the second, it's to reduce the deterioration of their health risks in the future for patients, for example AECOPD repeated attacking (You, 2013). Therefore, clinicians should pay attention to the short-term and long-term effect of AECOPD patients.

At present, the target of AECOPD is to relieve symptoms, improve exercise ability, improve health status, prevent disease progression, prevent acute exacerbation and reduce mortality. At present, the target of AECOPD is to relieve symptoms, improve exercise ability, improve health status, prevent disease progression, prevent acute exacerbation and reduce mortality.

First of all, it's important to reduce the degree of acute exacerbation of patients. If the patient is asthma serious, it should ease the symptoms of dyspnea. 2011 COPD (Tie, 2012) global strategy that was published by GOLD pointed out that the treatment of acute exacerbations in the symptoms of patients with the same time should also prevent the occurrence of acute exacerbation. However, the degree of awareness of a lot of patients was not enough, so you need to prompt the doctor, in addition to alleviate the symptoms, to prevent the occurrence of patients again AECOPD. A lot of patients were admitted

to hospital shortly after discharge, because of the lack of appropriate COPD stable treatment. So the doctor told patients the stability of the drug clearly when they discharged and urged patients to adhere to medication, so it can ease the symptoms and prevent recurrence.

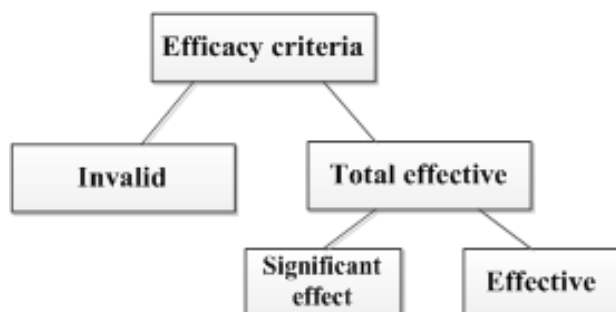


Fig. 4: Efficacy criteria

The drug therapy of AECOPD

Bronchial dilatation agent--relieving respiratory spasm was an important link to improve the symptom of patients and improve the survival rate. AECOPD treatment should be appropriate to increase the dose, frequency, etc. The main drugs include: β_2 receptor agonist, anti-choline and theophylline drugs. β_2 receptor agonist: the use of clinical commonly β_2 receptor agonist is divided into two kinds of short - and long-term effects. Short acting β_2 agonist agent is commonly used drugs such as salbutamol and special cloth him forest and long-acting β_2 agonists was salmeterol and formoterol. The short-acting β_2 -receptor agonist was effective for the treatment of AECOPD. However, it should avoid the sensitivity of the β_2 receptor agonist which can cause the cell membrane β_2 receptor to be down regulated in a long time. Anticholinergic drugs: Isopropyl supporting bromide and tiotropium bromide with clinical commonly were used anticholinergic drugs. Tiotropium bromide can be selective in choline M_1 and M_3 to receptors and bronchial dilatation significantly strengthened, reduce the adverse effects with some of the anti-inflammatory effects for a long time. The patients with AECOPD who had not been treated with anti-choline agents can be treated with the inhalation of the anti-choline bromide or bromide, until the remission of the disease. Theophylline: Theophylline can make closed trapped gas volume reduction, increase respiratory muscle strength and efficiency, lessen the amount of airway inflammation and secretion, so as to relieve bronchial spasm and improve ventilation, which can dilate pulmonary vessels, increase myocardial contractility and improve right heart function. The low dose theophylline (theophylline concentration of plasma 10mg/L) also has anti-inflammatory and immune modulation, and has a synergistic effect on the anti-inflammatory of glucocorticoids. Doxofylline is a novel antitussive and antiasthmatic drug, which can through a variety of ways to reduce airway hyper responsiveness, relieve airway spasm of clinical curative effect and have good curative

effect for patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

Glucocorticoid: glucocorticoid has powerful anti-inflammatory effect. It can treat the patients of AECOPD with hormone therapy, which should improve the respiratory difficulties, improve FEV1, accelerate the improvement of an illness, significantly shorten the hospitalization time and delay the occurrence of the next AECOPD.

Antibacterial drugs: before the sputum culture, the doctor should have the experience in the treatment of the symptoms, the infection of the environment and the gram stain of the sputum smear gram of AECOPD, the nosocomial infection was mainly Gram-negative bacteria, and the infection of the hospital was mainly in gram positive bacteria, two drugs can be chosen for the treatment, the principle of treatment was generally the first selection of narrow spectrum of antibiotics, the selection of broad-spectrum should be alert to the secondary fungal infection (Hui *et al.*, 2006). Two kinds of antibiotics are used in the patients, and the treatment of Gram-negative bacteria is also focused on the treatment of Gram-negative bacteria.

Drug regimen-combined medication for the optimization

To prevent recurrence of AECOPD, we must pay attention to the treatment of the stable period. There are a lot of studies on how to prevent and cure the recurrence of AECOPD in patients. It has been proved that the preventive measures for oral antibiotics in the long term of oral administration in the long term are not desirable, because it not only has the related side effect of antibiotics, but also can easily induce the antibiotic resistance. COPD global strategy is also particularly stressed and prevention of AECOPD does not recommend oral antibiotics.

AECOPD is preventable, there are many methods to reduce the acute exacerbation and hospitalization times, such as smoking cessation, flu and pneumonia vaccines, inhaled long-acting bronchodilators or combined with inhaled corticosteroids, application of phosphodiesterase 4 inhibitors and so on.

In particular, stable phase of use of some bronchial dilation agents and inhaled corticosteroids (ICS) can prevent the occurrence of acute exacerbation of patients. The stable phase of patients even in the past have AECOPD, adhering to the medication will also make the degree of attack better than the original stage and reduce the number of attacks also decreased significantly. COPD global strategy proposed that patients with slow lung disease such as AECOPD prevention, it must adhere to the treatment in the stable period. One of the methods is the application of ICS combined with long-term bronchial

dilation agent, usually relieve symptoms and can also prevent AECOPD recurrence.

Clinical effect observation 1(2012.1-2013.1)

General information

100 patients with AECOPD from 2012.1-2013.1 were selected, including 63 males, 37 females, age from 57 to 87, the average of 65.2 years. The patients had COPD for 1 to 12 years, and the average was 6.1 years. All cases were consistent with diagnostic criteria about "Guidance for diagnosis and treatment of chronic obstructive pulmonary disease (2007 Revision)".

Grouping and treatment

The 100 patients were equally divided into control group and treatment group. There were no significant differences in age, gender and incidence between the 2 groups ($P > 0.05$) and it was comparable (seen in table 1). Both of the two groups use antibiotic anti-infection, cough and phlegm, antispasmodic drugs oral aminophylline, at the same time, according to the disease use anti heart failure, reducing the blood viscosity, correcting the electrolyte disorders, and expanding the comprehensive treatment such as blood vessel. The control group was treated with salbutamol sulfate solution (commodity name: Ventolin, GSK Co production, registration number: H20090087, specifications: 5mg/mL) 1mL, adding 4mL saline and atomizing inhalation, 10~15 min/time, twice/day, continuous treatment for 10 days. The treatment group was treated with aerosol inhalation of Combivent (Boehringer Ingelheim Pharmaceutical Co. Ltd. production, registration number: H20120544, specifications: 5mL/branch, contain ipratropium bromide 0.5 mg+ salbutamol sulfate 3 mg) 2.5mL, 10~15 min/time 3 time/day, and at the same time the patients were given with systemic intravenous glucocorticoid treatment 10 days. Patients were received 60mg methyl prednisolone (product name: Jia Qianglong, Pfizer SA production, registration number: H20130303, size: 40mg/ bottle) with intravenous injection of 1 to 3 times /d, and gradually reduce the whole course of 10 days.

Observation index and efficacy criteria

Dyspnea score. The details are as follows: 0 point, non-violent activities showed no shortness of breath (Miller-Larsson and Selroos 2006); 1st, brisk walking on the stairs, on the gentle feel shortness of breath; 2nd, because of dyspnea, walking speed is slower than their peers; 3rd points, continuous walking is more than 5 minutes after feeling shortness of breath; 4th, man walks more than 100m due to shortness of breath and is forced to stop activities; 5th, because of breathing difficulties and man cannot leave the house, or take off clothes, feel shortness of breath.

Arterial blood gas index. The arterial blood gas before and after treatment in 2 groups were observed, including

arterial oxygen partial pressure (PaO_2) and arterial carbon dioxide partial pressure (PaCO_2).

The 3 groups of patients before and after the treatment of pulmonary function index were observed, including vital capacity (VC), forced vital capacity (FVC), 1 second forced expiratory volume (FEV_1) and FEV_1/FVC , the recurrence rate and the incidence of complications of AECOPD were statistically analyzed in 2 groups.

Remarkable effect: Relieve cough, wheezing symptoms, sputum was significantly reduced, and pulmonary rales disappeared; effective: cough, pulmonary rales, sputum reduce and wheezing symptoms improved obviously; invalid: Cough, wheezing symptoms is without obvious improvement, sputum volume is decreased, and pulmonary rale has no improvement. Total effective = significant effective + effective (fig. 4)

STATISTICAL ANALYSIS

All data were statistically analyzed by SPSS 18. Count data used (%) to express, and the comparison between groups used χ^2 test. The measurement data were expressed in the standard deviation ($\bar{x} + s$).

RESULT

Comparison of dyspnea score between 2 groups before and after treatment. There was no significant difference in dyspnea scores (table 2) between the 2 groups before treatment ($P > 0.05$). The dyspnea score after treatment in the 2 groups were significantly lower than that before treatment, and the dyspnea score after treatment was significantly lower than that of the control group ($P < 0.05$).

Comparison of clinical efficacy of the two groups. The total effective rate of the treatment group was 96% significantly higher than that of the control group 76%, and the difference was statistically significant ($P = 0.008$) (table 3).

There was no significant difference in the blood gas indexes between the two groups before treatment ($P > 0.05$). The arterial blood gas indexes of the two groups such as PaCO_2 and PaO_2 were significantly better than before treatment, the improvement of the treatment group was significantly better than the control group, and the difference was statistically significant ($P < 0.05$) (table 4).

There was no significant difference in the pulmonary function index between the two groups ($P > 0.05$). The pulmonary function index of the two groups after treatment, FEV_1 , FEV_1/FVC accounted for the expected value was significantly better than before treatment. And the improvement of the treatment group was significantly

Table 1: Comparison of basic information

Group	n	Gender(men/women)	Age	Course of disease
Treatment	50	33/17	63.5±5.7	6.0±2.6
Contrast	50	30/20	66.9±6.3	6.3±3.4

Table 2: Comparison of dyspnea score between two groups before and after treatment ($\bar{x} \pm s$)

Group	Before treatment	After treatment
Treatment(50)	3.38±1.18	1.46±0.49 ^{*Δ}
Contrast(50)	3.32±0.97	2.26±0.58 [*]

*Compared with before treatment, P<0.05; Δ compared with the control group, P<0.05

Table 3: Comparison of clinical efficacy of the two groups Proportion (%)

Group	Significant effect	Effective	No effective	Total effective
Treatment(50)	19 (38.0)	29 (58.0)	3 (6.0)	49 (96.0)
Contrast(50)	14 (28.0)	24 (48.0)	13 (26)	38 (76.0)

Table 4: Comparison of the changes of arterial blood gas and pulmonary function in the two groups before and after treatment ($\bar{x} \pm s$)

Group	Time	PaO ₂ (mmHg)	PaCO ₂ (mmHg)	FEV ₁ /FVC(%)	FVC expected value
Treatment (50)	Before treatment	47.3±11.3	67.8±6.6	48.7±5.4	50.4±4.9
	After treatment	77.9±14.2 ^{*Δ}	45.2±6.5 ^{*Δ}	67.4±6.9 ^{*Δ}	63.3±4.1 ^{*Δ}
Contrast (50)	Before treatment	47.9±10.9	65.6±6.8	51.4±5.4	51.7±4.5
	After treatment	68.4±10.4 [*]	54.7±6.3 [*]	57.3±7.4 [*]	56.8±4.5 [*]

*Compared with the before treatment, P<0.05; Δ compared with the control group, P<0.05

Table 5: Comparison of the time of symptom relief and symptom relief in the two groups ($\bar{x} \pm s$)

Group	Cough remission time	Polypnea disappear time	Breathing disappear time	Pulmonary signs disappear time
Treatment (50)	2.12±0.73 [*]	2.44±0.79 [*]	2.66±1.25 [*]	5.23±2.58 [*]
Contrast (50)	3.56±0.82	4.35±0.67	4.68±1.42	7.98±2.61

*Compared with the contrast, P<0.05

Table 6: Average course of treatment for patients with COPD (days)

Group	number	Average treatment	t value	P value
Treatment	50	9.5±4.1	2.38	<0.04
Contrast	50	13.4±3.2		

No serious adverse reactions were found during the treatment for the two groups

Table 7: comparison of basic information of AECOPD patients in the 3 groups

Group	n	Gender (men/women)	age	Course of disease	Predictive value of VC(L)	Predictive value of FVC(L)	Predictive value of FEV ₁ (L)
Routine	30	19/13	64.7±14.3	5.8±4.4	3.89±0.26	3.75±0.19	2.65±0.16
Short treatment	30	16/12	65.9±16.8	5.5±4.9	3.88±0.16	3.73±0.22	2.69±0.14
Long treatment	30	17/13	68.6±15.5	5.7±4.2	3.82±0.17	3.78±0.18	2.61±0.11

better than the control group and the difference was statistically significant (P<0.05) (table 4). The treatment group of cough relief time, shortness of breath (Davies *et al.*, 2014), wheezing, pulmonary

Table 8: Lung function, recurrence rates and complications of AECOPD patients in 3 groups after treatment ($\bar{x} \pm s$, %)

Group	n	VC(L)	FVC(L)	FEV ₁ (L)	FEV ₁ /FVC	Recurrence rate	Complication
Routine	30	2.69±0.47	2.43±0.22	1.23±0.17	57.59±6.26	43.2	27.3
Short treatment	30	3.04±0.74*	2.78±0.56*	1.83±0.56*	65.63±6.58*	36.7*	26.4
Long treatment	30	3.15±0.78*	2.88±0.58*	1.84±0.47*	65.77±6.32*	38.4*	43.8*

*Compared with the conventional group, P<0.05

symptoms disappearance time were significantly shorter than that of the control group, and the differences were statistically significant (P 0.05) (table 5).

The average number of hospitalization days in treatment group was 10d, the average number of hospitalization days in control group was 15d, the number of treatment days in treatment group was significantly lower than that in control group (P<0.05)(table 6).

DISCUSSION

In patients with chronic obstructive pulmonary disease (COPD) in patients often have acute exacerbation (AECOPD), severe acute exacerbation of COPD occurs, serious complications occurred in COPD, respiratory failure or cardiac failure, pulmonary heart disease. Symptoms can be improved after treatment with these drugs. In the acute phase, there is no unified principle, the patient's drug selection. Therefore, timely and effective diagnosis and treatment of AECOPD to maintain the stability of chronic obstructive pulmonary disease, prevention and treatment of complications is important. In the acute exacerbation of chronic obstructive pulmonary disease, the treatment of bronchial dilation is also an important adjuvant therapy. Some studies suggest that the drug anticholinergic bronchodilator in the treatment of chronic obstructive pulmonary disease the most effective, because the vagal tone is reversible factors of airflow obstruction of COPD (Sonetti *et al.*, 2010). Compound isopropyl bromide solution and support each 2.5ml inhalation of ipratropium bromide and salbutamol sulfate solution composition containing 0.5mg 3mg combivent inhalation. Bronchodilator effect of ipratropium bromide and salbutamol sulfate additive effect, curative effect is better than that of single drug and aerosol inhalation. Patients can guarantee 2% to 12% doses to reach the lungs without any complex action, to complete, because good compliance, and to play its therapeutic role. The principle of rational use of glucocorticoids is to accurately understand the conditions of the inflammatory response, and to use appropriate dosage and treatment in an appropriate time. In this clinical observation, due to the long-term use of glucocorticoids, some patients with elevated blood pressure, blood glucose phenomenon. Guidelines for diagnosis and treatment of chronic obstructive pulmonary disease in the treatment of acute exacerbation of the treatment program must be inhaled bronchial dilation agent, but the application of systemic

hormone therapy is still controversial. The key point of contention is that glucocorticoids inhibit inflammatory reaction and inhibit the inflammatory reaction (Walters *et al.*, 2003), in the later stage of acute lung injury, glucocorticoid can aggravate the immune response caused by infection or multiple infections can lead to increased mortality. Therefore, in order to achieve a more rigorous clinical effect, and to find better treatments of combivent combined with glucocorticoid treatment can get better AECOPD patients, alleviate the suffering of the burden of the patients more AECOPD treatment improved. Clinical effect of the second observation.

Clinical effect observation 1(2013.2-2014.7)

General information

100 patients with AECOPD from 2013.2-2014.1 were selected, including 52 males, 48 females, age from 45 to 86, the average of 61.4 years. The patients had COPD for 1-10 years, an average of 5.6 years.

Grouping and treatment

100 patients were equally divided into conventional treatment group (conventional group), conventional treatment plus glucocorticoid treatment group (short-term group) and conventional treatment plus glucocorticoid treated group (long-term group). There were no significant differences in age, gender, incidence and basic lung function between the 3 groups (P>0.05) and with comparable (table 7). The conventional group was treated with atomization inhalation of ipratropium bromide. The short term group was treated with glucocorticoid for 5 days on the basis of conventional treatment. The first day, patients were received intravenous injection of 40mg methyl prednisolone, 2~7 days of oral prednisolone 40mg /d. The long term group was treated with glucocorticoid for 14 days on the basis of conventional treatment. The first day, patients were received intravenous injection of 40mg methyl prednisolone, 2~15 days of oral prednisolone 40mg /d. All patients were received broad-spectrum antibiotics at the same time with 7 days and were treated with oxygen and ventilation, followed up for 6 months.

Evaluation index

Three groups of patients were treated for sixth days and fifteenth days after the monitoring of pulmonary function. Including vital capacity (VC), forced vital capacity (FVC), 1 second forced expiratory volume (FEV1) and FEV1 /FVC, the recurrence rate and the incidence of

complications of AECOPD were statistically analyzed in 3 groups.

CONCLUSION

Chronic obstructive pulmonary disease is a common disease which is seriously harmful to human health, which seriously affects the quality of life of patients, and the mortality is high. COPD is a daily change that goes beyond the acute exacerbation of respiratory symptoms in patients with COPD and a large proportion of respiratory symptoms. This situation should improve the patient's symptoms, relieve clinical symptoms, ease the patient's acute attack, reduce the patient's future health risk. In this paper, shows that from 2012. 1 to 2014. 7 of patients with AECOPD 190 cases clinical observation results: the use of ipratropium bromide and glucocorticoid treatment of AECOPD can effectively improve the condition of patients with dyspnea, improve lung function, reduce symptoms and signs of remission time, shorten the hospitalization time. Its adverse reactions are less, so it is effective for the treatment of AECOPD. Combivent combined with small dose, in acute exacerbation of chronic obstructive pulmonary disease treated by glucocorticoid short course period (AECOPD), not only can achieve the effect of treatment of long process, but also reduce the incidence of complications, relieve the pain of patients, is worthy of promotion.

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