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Clinical efficacy and safety of cardio-selective β-receptor blocker in management of AECOPD complicated with right heart failure.

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Abstract

Aims: To assess the clinical efficacy and safety of administration of a low dosage of cardio-selective β-receptor blocker in treating Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) complicated with right cardiac failure.

Methods: In total, 100 AECOPD patients were randomly assigned into the experimental (n=50) and control groups (n=50). Patients in the control group received standard treatment according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD, 2013 edition). Based upon conventional therapy, those in the experimental group received oral administration of metoprolol tartrate tablets. All patients were followed up for 1 year.

Results: The Forced Expiratory Volume in one second (FEV1) did not significantly differ between two groups (both P>0.05). Prior to the treatment, no statistical significance was observed in heart rate between two groups (P>0.05), whereas heart rate in the experimental group was significantly improved (P<0.05). The length of hospital stay did not significantly differ (P>0.05). In the experimental group, 3 patients (6.3%) suffered from adverse events, and 4 (8.4%) in the control group (P>0.05). In the experimental group, the frequency of acute exacerbation, mortality rate and NT-proBNP level were significantly lower than those in the control group (all P<0.05). Before and after therapy, the scores of COPD Assessment Test (CAT) did not significantly differ between two groups (P>0.05).

Conclusion: Use of a low-dose cardio-selective β-receptor blocker can effectively alleviate AECOPD complicated with right heart failure, improve heart function and decrease the frequency of acute exacerbation. No severe adverse events are noted after administration of cardio-selective β-receptor blocker.

Keywords: Cardio-selective β-receptor blocker, AECOPD, Right-sided heart failure, Safety, Efficacy.

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a type of obstructive lung disease characterized by long-term poor air flow. The main symptoms include shortness of breath and cough with sputum production. The severity of COPD typically progresses and worsens over time. The annual mortality rate of COPD has been reported to be 142.5/100000 among the male Chinese and 136.1/100000 for female counterparts in 2000. The incidence rate of COPD in China has been increasingly elevated. It is estimated that the mortality rate of COPD tends to rank 3rd across the globe [1].

Advanced COPD probably leads to high pressure on the lung arteries, which strains the right ventricle of the heart [2]. This situation is referred to cor pulmonale, and leads to symptoms of leg swelling and bulging neck veins. COPD is more common cause of pulmonary hypertension and right-sided heart failure. Cardio-selective β1-receptor blocker is a class of medications that are particularly used to manage cardiac arrhythmias and to protect the heart from a second myocardial infarction. They are also widely used to treat hypertension, although they are no longer the first choice for initial treatment for most patients. Nevertheless, it has been rarely applied to treat chronic cor pulmonale and right-sided heart failure because it probably provokes airway convulsion and worsens

relevant symptoms. Previous studies have demonstrated that cardio-selective β-receptor blocker exerts slight influence upon COPD patients. A meta-analysis of random case-control investigations evaluated the effect of cardio-selective β-receptor blocker upon patients with stable COPD and revealed no statistical significance before and after use of cardio-selective β-receptor blocker [2]. Dransfield et al. statistically compared the clinical efficacy and safety of selective and non-selective β-receptor blockers upon AECOPD patients and demonstrated that selective β-receptor blocker can significantly decrease the mortality rate [3]. Most retrospective investigations have analysed the effect of selective β-receptor blocker upon stable COPD complicated with myocardial infarction or left-sided heart failure [4-7]. The clinical efficacy and safety of cardio-selective β-receptor blocker in the management of AECOPD complicated with right-sided heart failure have been seldom assessed.

In this study, 100 AECOPD patients complicated with right-sided heart failure admitted to our hospital between July 2013 and July 2015 were recruited and administered with a low-dosage cardio-selective β-receptor blocker. Clinical efficacy and safety of cardio-selective β-receptor blocker upon this disease were evaluated in this case-control study.

Materials and Methods

Ethics approval

The study procedures were approved by the ethics committee of the First People's Hospital of Shuangliu District, Chengdu, China. All enrolled patients have signed the written informed consents. The physicians have informed all participants with the potential risk and remedial treatment.

Inclusion criteria

Patients who were diagnosed with AECOPD according to the GOLD standard (FEV1/FVC<70% after inhalation of bronchodilators) were enrolled. Those complicated with chronic cor pulmonale in cardiac functional decompensatory period were recruited. Those with NT-proBNP>1800 pg/ml and sinus tachycardia with a heart rate>100 beats/min were included in this clinical trial.

Exclusion criteria

Those complicated with coronary atherosclerotic heart disease, hypertensive cardiopathy or myocardial illnesses; those presenting with AECOPD due to use of cardio-selective β-receptor blocker; those with sick sinus syndrome; those with systolic blood pressure<100 mmHg; those with left-sided heart failure detected by color ultrasound; those failed to continue use of cardio-selective β-receptor blocker due to chest tightness and heart failure exacerbation; those failed to obey physicians' advice during subsequent follow-up; those voluntarily discontinued the study.

Methods

Clinical treatment: According to the COPD standard, patients in the experimental group were administered with cardio-selective β-receptor blocker (metoprolol tartrate, AstraZeneca, UK). Those with alleviated chest tightness and no pulmonary rhonchus were supplemented with cardio-selective β-receptor blocker. Relevant parameters were assessed by two chief physicians who were blind to the study design. The severity of chest tightness symptoms and lung signs was evaluated when a dose of 6.25, 12.5 and 25 mg (bid) was orally administered in sequence, respectively. In the control group, patients were given with control placebo (starch). Those with alleviated chest tightness and no pulmonary rhonchus were supplemented with the placebo. The dosage use and evaluation of relevant symptoms were performed as previously described in the experimental group.

Clinical parameters

Short-term clinical efficacy and safety included length of hospital stay, adverse events (chest tightness and lung rhonchus); long-term clinical efficacy and safety during 1-year follow-up included FEV1, CAT score, heart rate, the frequency of acute exacerbation, NT-proBNP level and mortality rate. CAT scale consisted of six subjective parameters including sputum, cough, energy, chest distress, emotion and quality of sleep, and daily physical activity and endurance ability. CAT score ranged from 0 to 40: 0-10 referred to slight influence, 11-20 indicated moderate influence, 21-30 represented severe influence and 31-40 reflected extremely severe influence. A change in CAT score of ≥ 2 points indicated statistical significance.

Statistical analysis

SPSS 19.0 statistical software was used for statistical analysis (SPSS Inc., Chicago, USA). Measurement data were expressed as mean ± standard deviation. Normally-distributed data were statistically compared by using t-test. Abnormally-distributed data were processed by Mann-Whitney test. Enumeration data were statistically analysed by chi-square test or Fisher's exact test. A P value of less than 0.05 was considered as statistical significance.

Results

Baseline data

A total of 100 AECOPD patients admitted to The First People's Hospital of Shuangliu District, Chengdu between July 2013 and July 2014 were recruited in this clinical trial. Fifty patients, 26 male and 24 female, aged 45 to 85 years with a mean age of 74.16 ± 5.95 years, were assigned into the experimental group. In the control group (n=50), 23 patients were male and 27 female, aged from 44 to 84 years, 74.82 ± 6.26 years on average. No statistical significance was observed in the baseline data between two groups (all P>0.05). After corresponding treatment, all participants were followed up for

1 year. Among 100 AECOPD patients, 7 cases were lost to the follow-up including 3 in the experimental group and 4 in the control group. Two cases were lost to contact due to changes of resident place and telephone number. Six patients were transferred to other hospitals and lost to subsequent follow-up, as illustrated in Table 1.

Table 1. *Comparison of baseline data between the experimental and control groups.*

			Gender	
Group	**Cases (n)**	**Age (year, mean ± S)**	**Male**	**Female**
Experimental group	50	74.16 ± 5.95	26	24
Control group	50	74.82 ± 6.26	23	27
T value	-	-0.54	1.293	
P value	-	0.59	0.255	

Comparison of short-term clinical efficacy

In the experimental group (n=47), the mean length of hospital stay was 13.19 ± 2.16 d and 12.93 ± 2.25 d in the control group. No statistical significance was observed in the length of hospital stay between two groups (t=0.562, P>0.05), as illustrated in Table 2. In the experimental group, 1 patient (2.1%) suffered from chest tightness, and 2 (4.2%) in the control group. In the experimental group, 2 cases (4.2%) reported lung rhonchus, and 2 (4.2%) in the control group. The incidence of adverse events was 6.3% in the experimental group, and 8.4% in the control group.

Comparison of long-term clinical efficacy

As illustrated in Table 2, the frequency of acute exacerbation was calculated as 1.64 ± 0.94 times per year in the experimental group, which was significantly lower compared with (2.04 ± 0.82) times per year in the control group (t=-2.215, P<0.05). In addition, the mortality rate of AECOPD patients was 0 in the experimental group, whereas 4.3% in the control group. Before and after corresponding treatment, the FEV1 was reduced by 1.13 ± 1.15, and 1.15 ± 1.15 in the control group. No statistical significance was noted in terms of the FEV1 between two groups (t=-0.102, P>0.05). Before and after administration, the heart rate was declined by 9.06 ± 8.18 in the experimental group, which significantly differed from -3.67 ± 11.13 in the control group (t=-6.278, P<0.05). Before and after treatment, the NT-proBNP level was decreased by 1795.3 ± 1141.42 pg/ml in the experimental group, whereas -926.02 ± 1600.52 pg/ml in the experimental group. Mann-Whitney test revealed statistical significance in the NT-proBNP level between two groups (P<0.05), as revealed in Table 2.

Table 2. *Comparison of multiple parameters between the experimental and control groups.*

Parameters	**Experimental group**	**Control group**	**T value**	**P value**
Frequency of acute exacerbation (times, mean ± S)	1.64 ± 0.94	2.04 ± 0.82	-2.215	0.029
FEV1 difference (mean ± S)	1.13 ± 1.15	1.15 ± 1.15	-0.102	0.919
Heart rate difference (beats/min)	9.06 ± 8.18	-3.67 ± 11.13	-6.278	0
NT-proBNP level (Pg, mean ± S)	1795.3 ± 1141.42	-926.02 ± 1600.52	-6.278	0
Length of hospital (day, mean ± S)	13.19 ± 2.16	12.93 ± 2.25	0.562	0.576

Comparison of CAT score between the experimental and control groups

Prior to treatment, slight influence was imposed in 17 patients (34%), moderate influence in 15 (30%) and severe influence in 14 (28%) and extremely severe influence in 4 (8%) in the experimental group. In the control group, slight influence was reported in 16 cases (32%), moderate influence in 16 (32%), severe influence in 15 (30%) and extremely severe influence in 3 (6%). Fisher's exact test revealed no statistical significance between the experimental and control groups (t=0.333, P>0.05). Following corresponding treatment, slight influence was imposed in 10 (21.3%), moderate influence in 16 (34%) and severe influence in 15 (31.9%) and extremely severe influence in 6 (12.8%) in the experimental group. In the control group, slight influence was reported in 9 cases (19.6%), moderate influence in 17 (37%), severe influence in 16 (34.8%) and extremely severe influence in 4 (8.6%). Fisher's exact test demonstrated no statistical significance between the experimental and control groups (t=0.567, P>0.05), as illustrated in Table 3.

Table 3. *Comparison of CAT score between the experimental and control groups before and after treatment.*

Group	**Cases (n)**			
	Slight influence	**Moderate influence**	**Severe influence**	**Extremely severe influence**
Experimental group	10 (21.3%)	16 (34%)	15 (31.9%)	6 (12.8%)

Control group	9 (19.6%)	17 (37%)	16 (34.8%)	4(8.6%)
Fisher' exact test (P=0.952)				

Discussion

In this clinical trial, 100 patients diagnosed with AECOPD complicated with right-sided heart failure admitted to our hospital between July 2013 and July 2014 were recruited and followed up for 1 year. Half of these patients were administered with a low-dosage cardio-selective β-receptor blocker. Clinical efficacy and safety of cardio-selective β-receptor blocker upon this disease were comprehensively evaluated in this case-control study. The results revealed that CAT score and FEV1 (%) did not significantly differ between the experimental and control groups before and after corresponding treatment, which were consistent with previous findings. Salpeter et al. [2] performed a meta-analysis of 17 relevant studies in which the effect of cardio-selective β-receptor blocking agent upon lung function of patients with mild to severe COPD was assessed. The findings suggested that continuous administration of cardio-selective β-receptor blocking agent does not induce significant decline in the pulmonary function. Previous studies have [8-13] demonstrated that β-receptor blocking agent is an efficacious and safe approach in the treatment of moderate to severe COPD complicated with heart failure. In this case-control study, the length of hospital stay did not significantly differ between the experimental and control groups. Use of cardio-selective β-receptor blocker fails to prolong the length of hospital stay. During the therapy, short-term adverse events included chest tightness in 7 cases, lung rhonchus in 6, heart failure exacerbation in 5 and lung rhonchus in 4 cases. In the experimental group, only 3 patients (6.3%) developed adverse events after corresponding treatment. In the control group, 4 cases (8.4%) reported the incidence of adverse events. The incidence of short-term adverse events did not significantly differ between the experimental and control groups. Subsequent stratified analysis demonstrated that relevant symptoms were significantly mitigated after administration of alternative antibiotics. These adverse events probably result from host infection and poor control of heart failure symptoms.

Compared with the control group, the heart rate of patients in the experimental group was significantly improved since cardio-selective β-receptor blocker could slow the heart rate, reduce the myocardial oxygen consumption and improve myocardial restructuring. AECOPD patients present with more evident myocardial hypoxia. Consequently, the heart rate was significantly slowed down after administration of cardio-selective β-receptor blocker. In the experimental group, the frequency of acute exacerbation and mortality rate were significantly lower than those in the control group. Upon the acute exacerbation, the NT-proBNP level in the experimental group was lower compared with that in the control group, which was consistent with previous findings [14]. They proposed that use of cardio-selective β-receptor blocker can significantly reduce the frequency of acute exacerbation for patients diagnosed with grade III and IV COPD [15]. Consequently, regardless of the severity of COPD, use of selective β-receptor blocker is able to considerably decrease the incidence of acute exacerbation of COPD. Moreover, selective β-receptor blocker plays a vital role in alleviating the severity of COPD [16]. COPD primarily occurs in the population aged above 40 years, which is defined as a high risk of cardiovascular diseases. The findings in this case-control study demonstrated that use of β-receptor blocker could significantly decrease the frequency of acute exacerbation of COPD and improve the heart function in COPD patients complicated with right-sided heart failure. It is assumed that administration of selective β-receptor blocker probably yields clinical benefits for those with cardiovascular diseases. Moreover, moderate and severe COPD patients were recruited in this investigation and administered with β2-receptor stimulating agent for a relatively long period. Thus, use of cardio-selective β-receptor blocker probably decreases the incidence of adverse events related to the cardiovascular diseases, thereby enhancing clinical prognosis.

Conclusion

Taken together, application of a low-dose cardio-selective β-receptor blocker can significantly alleviate AECOPD complicated with right-sided heart failure and improve the heart function. In short-term period, it does not affect the clinical symptoms and length of hospital stay. In the long term, it imposes no significant effect upon the lung function. In addition, use of cardio-selective β-receptor blocker can slow down the heart rate, reduce myocardial oxygen consumption, decrease the frequency of acute exacerbation of COPD and decrease the NT-proBNP level, thereby enhancing the clinical prognosis of AECOPD patients complicated with right-sided heart failure.

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Conflict of Interest

All authors declare no conflict of interests.

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