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ORIGINAL RESEARCH

Optimization of Nebulized Budesonide in the Treatment of Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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Rui Zhang*
Jiechen Zhu*
Yanan Liu*
Yuanqin Li
Wenjing Liu
Maowei Zhang
Bi Chen
Shuyang Zhu

Department of Respiratory Medicine, Affiliated Hospital of Xuzhou Medical College, Xuzhou, Jiangsu, People's Republic of China

*These authors contributed equally to this work

Background: Clinical studies have suggested nebulized budesonide (NB) as an alternative to systemic corticosteroids for patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). However, the optimal budesonide dose for AECOPD remains unclear.

Objectives: To compare the efficacy and safety of different doses of NB in the management of AECOPD.

Patients and Methods: A total of 321 AECOPD patients with moderate-to-severe exacerbation were randomly divided into three groups and treated with NB. The low dose group (L) was given 4 mg/day (n=95, 1 mg Q6h), while high-dose group 1 (H1, n=111, 2 mg Q6h) and high-dose group 2 (H2, n=115, 4 mg Q12h) were given 8 mg/day. Patients also received routine treatment including oxygen therapy, expectorant, nebulization bronchodilators, antibiotics, and fluid rehydration. The COPD assessment test (CAT), lung function, and artery blood gas were evaluated before and after 3 hrs and 5 days of treatment. In addition, hospital stay, frequency of acute exacerbations within 3 months of discharge, and adverse events during treatment were compared.

Results: H1 and H2 showed improved spirograms and CAT score faster than L. In H2, forced expiratory volume in 1 s (FEV_1%) at 3 hrs and FEV_1%, forced expiratory flow after 50% of the forced vital capacity has been exhaled ($FEF_{50\%}$), mean forced expiratory flow between 25% and 75% of forced vital capacity ($FEF_{25-75\%}$) and CAT score at 5 days were significantly improved compared to L. FEV_1% improved most in H2, moderately in H1, and least in L, with significant differences between groups at 5 days. No differences between groups were observed in adverse effects, hospital stay, and frequency of exacerbations within 3 months of discharge.

Conclusion: Compared to the conventional dose (4 mg/day), a high dose (8 mg/day) of NB improved pulmonary function and symptoms more effectively in the early treatment of AECOPD, especially when given as 4 mg twice daily.

Keywords: obstructive pulmonary disease, exacerbation, nebulized budesonide, dose, pulmonary function

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic and progressive disease. The 2016 Global Burden of Disease study estimated that worldwide, COPD caused 2.93 million deaths[1] and affected 65 million people.[2] COPD caused more deaths than any other chronic respiratory disease[1] and was the third leading cause of death worldwide in 2016.[3] The 2014 Global Burden of Lung Disease study showed that 56% (38.6 billion euros) of the European Union expenditure on respiratory diseases

Correspondence: Shuyang Zhu
Department of Respiratory Medicine, Affiliated Hospital of Xuzhou Medical College, Xuzhou, West Huaihai Road #99, Xuzhou 221000, People's Republic of China
Email shuyangzhu@126.com

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was spent on COPD.[4] In the United States, medicaid incurred $2118/year in incremental costs due to COPD.[5]

Acute Exacerbation of COPD (AECOPD) is defined as an acute deterioration of respiratory symptoms requiring additional treatment.[6] In COPD patients, exacerbations typically occur 0.5–3.5 times each year,[7] and cause decreased quality of life, frequent hospitalizations, rapid lung function decline, and increased mortality, disability rate, and healthcare costs.[8–11] In the United States, the median cost of inpatient care for AECOPD was estimated at $5844 per patient in 2010.[12] The management of AECOPD must be improved.

Systemic corticosteroids are recommended in the treatment of AECODP by almost all international guidelines.[6,13,14] However, because COPD patients are often elderly and relatively immobilized, high doses and frequent use of systemic corticosteroids[15,16] may cause increased complications, such as osteoporosis, hyperglycemia, anxiety, depression, and the risk of infection.[17–20] Recently, clinical studies and Meta-analysis have shown that nebulized budesonide (NB) is as effective as systemic corticosteroids in controlling nonacidotic AECOPD, as evaluated by clinical symptoms, lung function, and blood gas analysis. Furthermore, NB treatment reduces side effects[17–22] and medicine costs[23] compared to systemic corticosteroids. GOLD guidelines suggest NB as a suitable alternative to systemic corticosteroids in the treatment of exacerbations in some patients.[6]

In patients with acute asthma, FEV_1 improved significantly after NB alone for 3 hrs,[24] and different frequency and doses of budesonide have shown differences in improving pulmonary function and symptoms.[25–27] To some extent, the pathogenesis of airway inflammation in AECOPD and acute asthma is similar, and the treatment of AECOPD with NB and bronchodilators is promising. Because few studies have systematically investigated the frequency and dose of NB in AECOPD management, optimal treatment parameters are unknown.

In this study, we aimed to study the efficacy and safety of NB administered at different frequencies and doses for managing AECOPD. We evaluated CAT score, pulmonary function, blood gas analysis, hospital stay, frequency of exacerbations within 3 months after discharge, and adverse effects during treatment.

Materials and Methods

Patients

We prospectively enrolled AECOPD patients hospitalized in the Department of Respiratory Medicine at the Affiliated Hospital of Xuzhou Medical University from October 2017 to May 2019. Patients were randomly divided into three groups: a low dose group (group L, 1 mg Q6h) received 4 mg/day, while high-dose group 1 (group H1, 2 mg Q6h) and high-dose group 2 (group H2, 4 mg Q12h) received 8 mg/day. Patients provided written informed consent, the study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the ethics committee of the center (ID: XYFY2017-KL148).

Inclusion criteria were as follows: age more than 50 years; smoking history of at least 20 pack-years; meet GOLD diagnostic criteria for COPD[6] (show major COPD symptoms [chronic cough, expectoration, and/or dyspnea] and a history of exposure to risk factors, exhibit persistent airflow limitation, spirometry shows the presence of a post-bronchodilator $FEV_1/FVC < 0.70$), and diagnosed with AECOPD[6] (have an acute worsening of respiratory symptoms including dyspnea, chronic cough, or sputum production that results in additional therapy in COPD patients).

Patients were excluded from the study if they: had a personal history of asthma, allergic rhinitis, or atopy; had cancer, serious heart, liver, kidney, gastrointestinal diseases, or hepatorenal endocrine disease; were at risk of acute respiratory failure requiring mechanical ventilation or admission to the intensive care unit (ICU); had deterioration caused by specific reasons such as pneumonia, pneumothorax, or congestive heart failure; or had been exposed to systemic corticosteroids in the 30 days before admission.

Treatment During Hospitalization

Patients with AECOPD were randomly assigned to receive 4 mg NB per day (group L, 1 mg Q6h) or 8 mg NB per day (group H1, 2 mg Q6h; group H2, 4 mg Q12h). Patients also received routine treatments including oxygen therapy to ensure $SaO_2 > 90\%$, expectorant, nebulization bronchodilator (Compound Ipratropium Bromide Solution for Inhalation, 1 mg Q6h), antibiotics and fluid rehydration. No other steroids were used during the treatment period.

NB (1.0 mg/2 mL, Pulmicort respules®, AstraZeneca, London, England) and compound ipratropium bromide (0.5 mg ipratropium bromide and 3 mg salbutamol sulfate, Combivent®, Boehringer Ingelheim, Ingelheim, Germany) were driven by oxygen power with an oxygen flow rate of 4 to 6 L/min.

Clinical Efficacy

CAT score, lung function, and blood gas analysis (PaO_2 and $PaCO_2$) were evaluated before treatment, 3 hrs after nebulizing, and after 5 days of treatment. Lung function

was evaluated by FVC%, FEV_1%, FEV_1/FVC%, $FEF_{50\%}$, $FEF_{25–75\%}$, and residual volume (RV)/total lung capacity (TLC). Arterial blood gas analysis was performed while breathing room air at rest.

Length of hospital stay and frequency of acute exacerbations within 3 months after discharge were also compared. Exacerbation after discharge was defined as an unscheduled visit to any medical unit due to increase in cough, purulent sputum, or dyspnea. Patient status after discharge was assessed by monthly phone calls for 3 months.

Adverse Events

Adverse events included hoarseness, hyperglycemia, and sleep disruption. In addition, pulmonary function, COPD deterioration, ICU admission, early discharge, and patient withdrawal for any reason were monitored and recorded.

Statistical Analysis

Clinical data were analyzed using SPSS 22.0 software. All quantitative data were expressed as mean ± SD. ANOVA and paired t-tests were used to compare changes in continuous variables between and within groups, respectively. All categorical data were expressed as rate and percentage, with Chi-square tests used to compare groups. A two-sided p-value < 0.05 was considered statistically significant.

Results

A total of 378 patients were enrolled and randomly assigned to the three groups. During the study, 57 patients were excluded due to uncompleted pulmonary function tests (n=24), rapid deterioration or admission to ICU (n=10), early discharge (n=9), or refusing to cooperate with treatment (n=14). Dropout rates were similar among the three groups (17.2% L, 15.7% H1, 15.4% H2). Groups L, H1, and H2 had 95, 111, and 115 patients complete treatment, respectively.

General Characteristics

The three groups of patients did not have significant differences in general characteristics, including age, gender, current smoking index, time of exacerbation, eosinophil count, glucose, complications, concomitant treatment before randomization, CAT score, PaO_2, $PaCO_2$, and lung function (p>0.05 for all parameters) (Table 1).

Short-Term Clinical Efficacy

Compared to before nebulization, PaO_2 was significantly improved in all three groups after 5 days (p<0.001 for all parameters). There were no significant differences between groups at 3 hrs or 5 days (p=0.529 and p=0.748, respectively) (Table 2).

At 5 days, CAT scores had improved in the L, H1, and H2 groups by 5.3 ± 2.1, 5.9 ± 2.3, and 6.4 ± 2.6, respectively, with significant improvements in all groups compared to baseline (p=0.021, p=0.038 and p=0.009, respectively). The H2 group showed significantly greater changes compared to group L (p=0.048) (Table 3).

Although initial spirometric parameters were similar between groups, absolute values after 3 hrs and 5 days were higher in H2 than L and H1. In groups L, H1, and H2, FEV_1% improved 0.7 ± 0.8%, 1.1 ± 0.7%, and 1.4 ± 0.5% at 3 hrs, and 3.3 ± 4.7%, 4.3 ± 4.6%, and 5.6 ± 5.4% at 5 days, respectively. The H2 group showed significant improvement in FEV_1% at 3 hrs (p=0.033), and there were significant differences between the three groups at 5 days (p<0.05 for

Table 1 General Characteristics of Patients at Admission[‡]

	L[#]	H1["]	H2[+]
Age (yr)	69.1 ± 8.9	68.2 ± 8.2	67.3 ± 7.6
Sex M/F	73/12	97/14	109/16
Current smokers (%)	23 (23.9%)	37 (33.3%)	40 (34.8%)
Time of exacerbation (d)	12.6 ± 11.4	13.5 ± 13.2	11.9 ± 9.7
Eosinophil count (*10^6/L)	184 ± 312	156 ± 227	124 ± 108
Glucose (mmol/L)	6.6 ± 2.8	6.6 ± 2.3	5.8 ± 1.3
Complications (%)			
Coronary	8 (9.4%)	12 (10.8%)	13 (10.4%)
Hypertension	16 (18.9%)	19 (17.1%)	22 (17.6%)
Diabetes	8 (9.4%)	7 (6.3%)	6 (4.8%)
Atrial fibrillation	6 (7.1%)	8 (7.2%)	10 (8%)
Concomitant Treatment Before Randomization (%)			
ICS	36 (38%)	40 (36%)	49 (39%)
LABA	39 (41%)	41 (37%)	49 (39%)
LAMA	51 (54%)	55 (50%)	60 (52%)
CAT score	15.4 ± 4.6	15.3 ± 5.8	14.3 ± 4.1
PaO_2 (mmHg)	65.3 ± 12.7	65.6 ± 13.1	63.4 ± 15.4
$PaCO_2$ (mmHg)	44.4 ± 8.7	45.0 ± 7.6	43.9 ± 5.6
Spirogram			
FVC% pred	54.5 ± 8.9	55.8 ± 10.3	56.1 ± 9.5
FEV_1% pred	56.7 ± 5.4	51.2 ± 7.5	53.0 ± 9.4
FEV_1/FVC (%)	55.3 ± 6.8	49.2 ± 7.9	53.8 ± 9.3
$FEF_{50\%}$ pred	19.4 ± 8.7	17.5 ± 9.5	18.8 ± 9.1
$FEF_{25–75\%}$ pred	18.3 ± 8.6	18.6 ± 7.3	19.4 ± 8.8

Notes: [‡]Values are mean ± SD or number (%). [#]1 mg Q6h; ["]2 mg Q6h; [+]4 mg Q12h.

Abbreviations: M, male; F, female; ICS, inhaled corticosteroids; LABA, long-acting β_2 agonists; LAMA, long-acting anticholinergic drugs; CAT, COPD assessment test; PaO_2, arterial oxygen tension; $PaCO_2$, arterial carbon dioxide tension; FVC, forced vital capacity; pred, predicted; FEV_1, forced expiratory volume in 1 s; $FEF_{50\%}$, forced expiratory flow after 50% of the FVC has been exhaled; $FEF_{25–75\%}$, mean forced expiratory flow between 25% and 75% of FVC; RV, residual volume; TLC, total lung capacity.

Table 2 Artery Blood Gas After Hospitalization‡

Characteristics	Group+	Baseline	3 h	5 d
PaO_2 (mmHg)	L	65.3 ± 12.7	63.5 ± 13.5	72.1 ± 10.7*
	H1	65.6 ± 13.1	65.3 ± 15.6	74.7 ± 14.8*
	H2	63.4 ± 15.4	64.5 ± 14.9	76.2 ± 16.3*
$PaCO_2$ (mmHg)	L	44.4 ± 8.7	44.9 ± 9.8	45.6 ± 7.7
	H1	45.0 ± 7.6	44.7 ± 6.1	43.5 ± 6.1
	H2	43.9 ± 5.6	44.4 ± 6.2	43.4 ± 3.4

Notes: ‡Values are mean ± SD; +Group L received NB 1 mg Q6h, group H1 received NB 2 mg Q6h, and group H2 received NB 4 mg Q12h; *p<0.05 compared to baseline.
Abbreviations: PaO_2, arterial oxygen tension; $PaCO_2$, arterial carbon dioxide tension.

Table 3 CAT Scores After Hospitalization‡

Characteristics	Group+	Baseline	3 h	5 d
CAT score	L	15.4 ± 4.6	15.0 ± 5.3	9.5 ± 3.3*
	H1	15.3 ± 5.8	15.1 ± 4.8	9.0 ± 4.7*
	H2	15.3 ± 4.1	15.6 ± 5.1	8.2 ± 3.2*#

Notes: ‡Values are mean ± SD; +Group L received NB 1 mg Q6h, group H1 received NB 2 mg Q6h, and group H2 received NB 4 mg Q12h; *p<0.05 compared to baseline; # p<0.05 compared to group L.
Abbreviation: CAT, COPD assessment test.

all parameters). In addition, $FEF_{50\%}$ and $FEF_{25–75\%}$ for H2 at 5 days was significantly improved compared to L (p=0.022 and p=0.041, respectively) (Table 4).

The hospital stay among three groups was similar, with groups L, H1, and H2 averaging 6.5 ± 2.4 days, 6.2 ± 1.7 days, and 6.5 ± 4.7 days, respectively (p=0.895).

Long-Term Clinical Efficacy

During the 3 months after discharge, 59.3%, 61.6%, and 56.3% of patients in the L, H1, and H2 groups, respectively, used inhaled corticosteroids (ICS). At the same time, 62.6%, 65.0%, and 62.1% of patients used long-acting β_2 agonists and 69.9%, 68.2%, and 67.5% of patients used long-acting anticholinergic drugs, respectively. No differences were seen between groups (p>0.05 for all parameters). Exacerbation frequency was 0.17 ± 0.07 times in the L group, 0.11 ± 0.09 times in the H1 group, and 0.14 ± 0.12 times in the H2 group, with no significant differences between groups (p=0.513).

Adverse Events

Only 15.7%, 15.3%, and 16.5% of patients in groups L, H1, and H2 experienced adverse events, and there were no significant differences between groups in the rate of adverse events. In group L, six patients had hoarseness, four patients had hyperglycemia (three with diabetes), and

Table 4 Lung Function After Hospitalization‡

Characteristics	Group+	Baseline	3 h	5 d
FVC% pred	L	54.5 ± 8.9	54.6 ± 10.8	63.7 ± 11.2*
	H1	55.8 ± 10.3	56.0 ± 14.8	62.3 ± 10.7*
	H2	56.1 ± 9.5	56.4 ± 8.6	63.9 ± 11.8*
FEV_1% pred	L	52.7 ± 5.4	53.3 ± 6.8	58.6 ± 8.3*
	H1	51.2 ± 7.5	52.4 ± 9.7	57.3 ± 8.5*#
	H2	53.0 ± 9.4	54.9 ± 10.3 *#	61.7 ± 10.8*#
FEV_1/FVC	L	55.3 ± 6.8	56.7 ± 7.7	58.5 ± 6.7
	H1	52.2 ± 7.9	57.8 ± 8.7	56.6 ± 8.3
	H2	53.8 ± 9.3	58.7 ± 10.8	57.7 ± 8.1
$FEF_{50\%}$ pred	L	19.4 ± 8.7	19.6 ± 10.1	20.6 ± 12.4*
	H1	17.5 ± 9.5	16.1 ± 9.1	19.1 ± 11.1*
	H2	18.8 ± 9.1	19.0 ± 9.5	23.0 ± 13.2*#
$FEF_{25–75\%}$ pred	L	18.3 ± 8.6	18.2 ± 9.7	21.6 ± 7.6*
	H1	18.6 ± 7.3	19.6 ± 8.3	22.3 ± 6.6*
	H2	19.4 ± 8.8	20.5 ± 7.21	24.9 ± 5.5*#
RV/TLC	L	52.3 ± 8.5	53.69 ± 7.8	44.4 ± 6.2*
	H1	53.2 ± 6.4	54.19 ± 6.7	45.9 ± 8.3*
	H2	50.3 ± 7.4	52.15 ± 8.8	44.0 ± 7.1*

Notes: ‡Values are mean ± SD; +Group L received NB 1 mg Q6h, group H1 received NB 2 mg Q6h, and group H2 received NB 4 mg Q12h; *p<0.05 compared to baseline; # p<0.05 compared to group L.
Abbreviations: FVC, forced vital capacity; % pred, % predicted; FEV_1, forced expiratory volume in 1 s; $FEF_{50\%}$, forced expiratory flow after 50% of the FVC has been exhaled; $FEF_{25–75\%}$, mean forced expiratory flow between 25% and 75% of FVC; RV, residual volume; TLC, total lung capacity.

five patients had insomnia. In group H1, ten patients had hoarseness, three patients had hyperglycemia (three with diabetes), and four patients had insomnia. In group H2, twelve patients had hoarseness, five patients had hyperglycemia (four with diabetes), and two patients had insomnia (Table 5).

Discussion

In this study, we investigated the efficacy and safety of different doses of NB for managing AECOPD. The results demonstrated that 8 mg/day of NB effectively improves short-term clinical outcomes for AECOPD patients compared to 4 mg/day of NB. Additionally, among patients treated with 8 mg/day, NB administered 4 mg Q12h improved FEV_1% more effectively than when administered 2 mg Q6h within 3 hrs, suggesting that a high dose of budesonide rapidly improved pulmonary function and symptoms.

Our study showed that NB administered 8 mg/day more effectively improved pulmonary function and symptoms than when administered 4 mg/day. Relatively little information is available on clinical effects of different doses of budesonide in patients with AECOPD. Inconsistent with our data, Akgun[20] showed no differences in FEV_1 or PaO_2 improvement when comparing NB at 8 mg/day and 4 mg/day for 24 hrs, 48 hrs, and before hospital discharge. The inconsistent results may be due to the patient population and the follow-up time for evaluation. Akgun et al noted significant baseline differences in FEV_1 between groups, suggesting that the degree of airway obstruction was different in each group, which may bias the results to some extent. Moreover, Akgun et al studied a relatively small number of patients and did not study small airway function improvement after NB. Further research is needed to evaluate a larger sample of patients in multicenter clinical studies.

Few studies have investigated the efficacy of nebulizing the same dose of budesonide at different frequencies in patients with AECOPD. Our study found that, compared to 2 mg Q6h, NB administered 4 mg Q12h significantly improved FEV_1%, $FEF_{50\%}$, $FEF_{25-75\%}$, and CAT score at 5 days. Some studies[28,29] have shown that glucocorticoids affect both genetic and non-genetic pathways through cytoplasmic and cell membrane receptors, but its action process is initiated by a membrane-bound hormone receptor. A high hormone concentration is often required due to the small quantity and low binding affinity of cell membrane receptors, and higher doses hormone cause stronger effects. In vitro experiments have confirmed that budesonide atomization takes effect a few minutes after nebulization, and improves airway and lung function in patients with chronic airway inflammation within a few hours.[27] Only 3 hrs after 4 mg NB was administered with bronchodilators, FEV_1% significantly improved, reflecting the rapid effects of corticosteroids. This intergroup difference is attributed to different corticosteroid doses because each group was treated with the same bronchodilator frequency and dose. Additionally, substantial evidence indicates that the combination of ICS and β_2 agonists has a synergistic effect. First, ICS improve β_2-adrenoceptor signaling by increasing β_2-adrenoceptor density[30] and reducing functional desensitization of the receptor.[31] Second, ICS inhibit inflammatory gene expression, which is enhanced by β_2 agonists.[32] Furthermore, ICS rapidly enhance the effects of bronchodilators, especially in combination with β_2 agonists,[33] which could be used as a rescue therapy in asthma and AECOPD.

To the best of our knowledge, few studies have evaluated the long-term efficacy of different doses of NB in AECOPD patients. In our study, the three treatment groups had similar exacerbation frequencies during the 3 months after discharge. Intravenous corticosteroids reduced the risk of acute exacerbation;[34] however, it is unclear whether increased doses of budesonide reduce the risk of acute exacerbation. Gunen et al[35] compared exacerbation frequency within 1 month of discharge in patients treated with placebo, NB 8 mg/day (1.5 mg Q6h), and intravenous prednisolone 40 mg/day. On the corticosteroid arms, these rates became almost half the rate in placebo arm, however these were not statistically significant. Ding et al[21] compared acute aggravation times with NB 6 mg/day (2 mg Q8h) and intravenous methylprednisolone 40 mg/day during the 12 months after discharge and found no significant differences between the two groups. However, this study did not account for different treatments after discharge between the two groups, limiting the interpretation of these results.

Table 5 Adverse Reactions in the Three Groups[‡]

Group +	Hoarseness	Hyperglycemia	Insomnia
L	6	4	5
H1	10	3	4
H2	12	5	2
χ^2	1.13	0.51	1.97
P	0.69	0.77	0.37

Notes: [‡]Values are number; [+]Group L received NB 1 mg Q6h, group H1 received NB 2 mg Q6h, and group H2 received NB 4 mg Q12h.

Administering NB 4 mg Q12h was more effective than 1 mg Q6h or 2 mg Q6h, but there were no significant differences in adverse effects and hospital stay among the three groups. Budesonide is a long-acting glucocorticoid, with a high binding affinity for the glucocorticoid receptor, small particle size, long pulmonary residence time, and lipid conjugation, which enhance its efficacy. Meanwhile, its low oropharyngeal exposure, in situ activation in the lung, negligible oral bioavailability, high protein binding, and rapid systemic clearance enhance its safety.[28] Taken together, these pharmacokinetic and pharmacodynamic characteristics give budesonide a high topical anti-inflammatory activity with a low level of systemic activity.[15,25,35] The incidence of adverse reactions in our study was similar to that observed in previous studies, indicating the safety of frequent high-dose NB. Moreover, giving the drug twice daily instead of four times daily could reduce medical costs and labor while increasing patient compliance.

This study was conducted in a single center with a small sample size and short follow-up time. Future multicenter studies with larger sample sizes and longer follow-up times are needed to better understand the use of high-dose budesonide in AECOPD as well as to understand its mechanism of action.

Conclusions

In conclusion, in patients with AECOPD, high-dose NB (4 mg Q12h) rapidly improved FEV_1%, small airway function, and exacerbation symptoms. Furthermore, high-dose NB treatment increased patient compliance, reduced manpower and material resources, and reduced medical resource consumption.

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Disclosure

The authors have no conflicts of interest to declare.

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