

Clinical Outcomes Of Using Nebulized Budesonide As The Initial Treatment For Acute Exacerbations Of Chronic Obstructive Pulmonary Disease: A Post-Hoc Analysis

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Purpose: The current guidelines recommend the use of systemic corticosteroids (SCS) as the optimal treatment for acute exacerbations of chronic obstructive pulmonary disease (AECOPD). The aim of this real-world study was to evaluate whether nebulized budesonide (NBS) could also be used as an initial treatment for AECOPD.

Patients and methods: AECOPD patients initially treated with NBS or SCS (oral/intravenous) were enrolled. A large-scale, long-term multicenter cohort study of AECOPD patients was performed to analyze outcomes for each treatment (NCT02051166).

Results: Initial NBS and SCS treatment resulted in similar outcomes in terms of improvements in FEV₁, PaO₂, SaO₂, and PaCO₂. Disease severity affected outcome similarly in both groups. When the groups were stratified according to whether the initial treatment was subsequently intensified or reduced, more intubation was seen in the groups in which initial treatment was intensified. NBS escalation and SCS reduction groups spent more days in the hospital. The NBS escalation group was associated with the highest medical expenditure and a relatively higher rate of new-onset pneumonia. The NBS maintenance/reduction group showed the lowest mortality rate between groups. Stratification according to initial PaCO₂ level showed more intubation in the groups with high initial PaCO₂ concentrations.

Conclusion: These results indicate that NBS may be used as an initial treatment in certain AECOPD patients, and further studies are needed to better define those most likely to benefit.

Keywords: nebulized budesonide, systemic corticosteroids, chronic obstructive pulmonary disease, AECOPD

Introduction

Chronic obstructive pulmonary disease (COPD) affects 65 million people worldwide and is responsible for 3 million deaths per year.¹ Most patients with COPD have at least one acute exacerbation of this disease (AECOPD) per year.^{2,3} Such exacerbations cause a decline in lung function, reduced quality of life, increased mortality, and an increased risk of further AECOPD.⁴ Treatment for AECOPD often requires hospitalization and is responsible for 60% of the global costs for COPD treatment.⁵

Systemic corticosteroids have been considered as the cornerstone of treatment for AECOPD^{2,6-8} and inhaled corticosteroids as useful for maintenance treatment thereafter to reduce the risk of further exacerbations.^{3,6} However, continued use of

systemic corticosteroids will cause steroid resistance and systemic side effects. Also, higher doses or longer periods of treatment for AECOPD do not improve outcomes, and the optimal dosage of systemic corticosteroids for AECOPD is unclear.^{1,7,9}

The use of nebulized instead of systemic corticosteroids to treat AECOPD would theoretically confine the anti-inflammatory action to the lung and avoid the undesirable systemic effects associated with oral or intravenous corticosteroid administration. In clinical practice, both nebulized budesonide (NBS) and systemic corticosteroids (SCS) are used for the initial treatment of AECOPD. A number of comparisons of NBS and SCS treatment of AECOPD have reported similar outcomes.^{2,10–13} To date, no study has been conducted on the results of initial NBS and SCS usage in general clinical practice. In the current report, we hypothesized that initial NBS and SCS, as used for AECOPD in current clinical practice, would give similar results. Our aim was to evaluate the real-world status of initial NBS and SCS usage in AECOPD in China and to determine what pre-treatment patient characteristics would potentially suggest the suitability of using NBS rather than SCS as initial AECOPD treatment.

Methods

Study Design And Patient Selection

The current study was a post-hoc analysis of a subset of data collected from a large, retrospective non-interventional study in China of corticosteroid treatment of patients hospitalized for AECOPD (NCT02051166).¹⁴ Patients were selected according to the initial therapy they received: NBS alone or SCS (oral/intravenous) alone. In our study, those who had received either NBS or SCS (oral/intravenous) for initial treatment of AECOPD were divided into two NBS groups (escalation group, defined as initial NBS followed by dose escalation or switch to SCS; maintenance group, defined as initial NBS followed by dose maintenance or reduction) and two SCS groups (maintenance group, defined as initial SCS followed by dose maintenance or escalation; reduction group, defined as initial SCS followed by dose reduction or switch to NBS). The demographics, clinical characteristics, and outcomes of the four groups were then compared to evaluate the real-world status of initial use of nebulized or systemic corticosteroids for the treatment of AECOPD and to determine which patients might benefit from initial NBS treatment. Since guidelines in China recommend antibiotic

treatment for patients with COPD, most patients included in this study (97%) received such treatment. Thus, antibiotic use may not affect the results of this study. In addition, these included patients who did not receive other therapy, such as diuretics, non-invasive ventilation, and high flow nasal canula.

The study was conducted in accordance with the guidelines of the Helsinki Declaration and was approved by independent ethics committees at all study sites prior to the start of the study, including the Peking University Third Hospital Medical Science Research Ethics Committee [2013-98-ssh-hxx (2013-100)]; Institutional Review Board of Beijing ChaoYang Hospital (IRB20140109); Institutional Review Board of Beijing Chaoyang Hospital, Capital Medical University [2014-02-21 (1)]; Ethics Committee of Beijing Tongren Hospital, Capital Medical University (TREC2014-03); Ethical Committee of Ruijin Hospital Affiliated to Shanghai JiaoTong University School of Medicine (2014-16); Huashan Hospital Institutional Review Board (2014-5-26); Ethical Committee of Shanghai Pulmonary Hospital (3-075HX); Ethical Committee of the Fifth People's Hospital of Shanghai (2014-016); Ethics committee of the Institutional Review Board of Shanghai Songjiang Central Hospital [201415-(2013-98-SSH-HXK)]; Ethics Committee of the Shanghai Minhang District Central Hospital of Ruijin Group [IRB20140325]; Peking University Third Hospital Medical Science Research Ethics Committee [2013-98-ssh-hxx (100)]; Ethics Committee of the First Affiliated Hospital, Nanjing Medical University, Jiangsu Province Hospital (IRB20140225); ERB of Guangzhou First People hospital (SOP-CX-011-03); Ethical Committee of Jiangsu Province (2014-SR-020); Committee of Nanjing General Hospital of Nanjing Military Command (2014NLY-003); Shandong Provincial Qianfoshan Hospital medical ethics committee (IRB20140211); Ethical Committee of The General Hospital Tianjin Medical University (IRB2013-088-01); Ethical Committee of The General Hospital of Shenyang Military Region (2014-#12); Ethics Committee of The First Hospital of Jilin University (140313-028); The Institutional Review Board of Second Hospital of Jilin University (2014-003); The Institutional Review Board of the Affiliated Hospital of Inner Mongolia University (2013MER-0002); The Institutional Review Board of the Affiliated Hospital of Inner Mongolia Medical University (2014-002); The Institutional Review Board of Hebei Provincial People's Hospital (Y-2014-01); Ethical Committee of The Second Hospital of Hebei Medical University (IRB20140314); The Institutional Review Board of China National Petroleum

Corporation Central Hospital (IRB20140109); Ethics Committee of Shanxi Provincial People's Hospital (IRB20140301); Shanxi Dayi Hospital Ethical Committee (IRB20140402); Ethics Committee of First Hospital of Shanxi Medical University (2014-13); The Institutional Review Board of Yuncheng Central Hospital of Shanxi Province (IRB20140116); Institutional Review Board of Henan Provincial People's Hospital (IRB20140308); Institutional Review Board of the People's Hospital of Zhengzhou University (IRB20140228); Ethics Committee of Anhui Medical University (PJ2014-02-04); Ethics Committee of Fujian Provincial Hospital (IRB20140516); Institutional Review Board and the Ethics Committee at Jiangxi Province People's Hospital (2014-004); Ethics Committee of Hubei Province Hospital of Traditional Chinese Medicine (2014-013); Ethics Committee Xiangya Hospital of Central-South University (IRB201403021); Ethical Committee of The Third Xiangya Hospital of Central South University (2014-IRB-022); IRB of West China Hospital (2014-1); Ethical Committee of the First Affiliated Hospital of Third Military Medical University, PLA (2014-10); Ethics Committee of Xinqiao Hospital, Third Military Medical University (2014026); Medical Ethics Committee of Shaanxi Provincial People's Hospital (2014-R003); IEC of Institution for National Drug Clinical Trials, Tangdu Hospital, Fourth Military Medical University (IRB2014013); Medical Ethics Committee of General Hospital of Ningxia Medical University (IRB20140306). Written informed consents were obtained from all patients prior to the start of the study.

Inclusion And Exclusion Criteria

The inclusion criteria in this study were as follows: (1) being older than 40 years; (2) being hospitalized due to AECOPD; and (3) having COPD for at least 3 months before the acute exacerbation. Exclusion criteria were (1) participation in any interventional study within 3 months of recruitment; (2) ongoing AECOPD during the recruitment period; (3) being discharged against medical advice; and (4) having a primary diagnosis for hospitalization other than AECOPD.

Variables

Demographic characteristics (age weight, height, BMI), smoking status, environment and drug exposure history, and intubation rate were taken from the study data, as well as the endpoint parameters listed below.

Primary endpoints were length of hospital stay (days) and change in FEV₁, arterial blood gases (PaO₂, SaO₂, PaCO₂), and pH after treatment. Secondary endpoints were rate of new-onset pneumonia during hospitalization and hospitalization expenses related to AECOPD.

Statistical Analysis

Continuous variables were presented as mean and standard deviation (SD), and categorical variables were presented as counts and percentages. One-way analysis of variance and Chi-square test were used to compare the difference between the four treatment groups with regard to intubation rate, mortality, rate of pneumonia, and rate of new-onset pneumonia. All statistical analyses were performed using SAS® version 9.4 (SAS Institute, Inc., Cary, NC, USA). Two-tailed $P < 0.05$ indicated statistical significance.

Results

Demographic Characteristics

Of the 3121 patients included in the current study, 756 (the NBS escalation group) were initially treated with NBS and then with dose escalation or a switch to SCS, while 1443 patients (the NBS maintenance/reduction group) were initially treated with NBS and then with dose maintenance or reduction. Some 404 patients (the SCS maintenance/escalation group) were initially treated with SCS and then with dose maintenance or escalation; the remaining 518 patients (the SCS reduction group) were initially treated with SCS and then with dose reduction or a switch to NBS.

Patients in the NBS groups were slightly younger and had lower baseline PaO₂ than patients in the SCS groups. Baseline PaCO₂ was lowest in the NBS maintenance/reduction group and highest in the SCS reduction group (Table 1).

Clinical Outcomes

Significant between-group differences were seen in length and expense of hospital stay, mortality, intubation, and improvement in FEV₁ (Table 2). Mortality and intubation rates were higher in the two groups needing treatment escalation. Patients in the NBS maintenance/reduction group and those in the SCS maintenance/escalation group spent fewer days in the hospital. FEV₁ improvement was worst (negative) in the NBS escalation group and best in the NBS maintenance/reduction group. Likewise, the NBS escalation group was associated with the highest

Table I Demographic Characteristics For NBS Or SCS By Intravenous Injection As Initial Treatment (Grouped By Further Treatment)

	Dose-Escalation Group (NBS Initial)	Dose Maintenance Or Reduction Group (NBS Initial)	Dose Maintenance Or Escalation Group (SCS Initial)	Dose-Reduction Group (SCS Initial)	P-Value
	(N=756)	(N=1443)	(N=404)	(N=518)	
	Mean ± SD				
Age (years)	72.9±9.3	72.5±9.7	73.2±9.6	73.0±9.3	0.01
BMI (kg/m ²)	22.1±3.5	22.2±3.9	22.0±3.3	21.9±3.4	0.85
COPD history (years)	9.3±8.7	9.1±8.9	10.3±9.7	11.6±10.1	0.61
AECOPD duration (days)	20.8±58.1	17.6±27.9	19.7±37.4	14.5±23.9	0.33
Baseline PaO ₂ (mmHg)	74.9±27.3	74.8±25.5	78.6±30.9	84.1±36.9	0.02
Baseline PaCO ₂ (mmHg)	51.3±15.6	48.0±14.3	51.2±18.9	52.7±18.9	<0.001
Baseline SaO ₂	91.6±8.3	91.8±8.4	91.7±9.1	92.8±8.0	0.06
Baseline pH	7.4±0.1	7.4±0.4	7.4±0.1	7.4±0.1	<0.001
	N (%)				
Sex					
Male	590 (78.0%)	1047 (72.6%)	308 (76.2%)	407 (78.6%)	0.67
Female	166 (22.0%)	395 (27.4%)	96 (23.8%)	111 (21.4%)	
Baseline pH categories					
<7.35	130 (17.2%)	224 (15.5%)	78 (19.3%)	85 (16.4%)	0.49
7.35–7.45	449 (59.4%)	917 (63.5%)	227 (56.2%)	314 (60.6%)	
>7.45	68 (9.0%)	167 (11.6%)	47 (11.6%)	59 (11.4%)	
Smoking status					
Never	206 (27.2%)	456 (31.6%)	129 (31.9%)	170 (32.8%)	0.38
Current	211 (27.9%)	365 (25.3%)	97 (24.0%)	122 (23.6%)	
Ever	327 (43.3%)	616 (42.7%)	172 (42.6%)	218 (42.1%)	
Living environment ^a					
Long-term passive smoking	48 (6.3%)	124 (8.6%)	26 (6.4%)	48 (9.3%)	0.49
Long-term exposure to occupational dust and gas fumes	58 (7.7%)	89 (6.2%)	18 (4.5%)	41 (7.9%)	
Air pollution ^b	232 (30.7%)	595 (41.2%)	182 (45.0%)	175 (33.8%)	
None of the above	402 (53.2%)	628 (43.5%)	182 (45.0%)	207 (40.0%)	

Notes: P-value is adjusted by site. ^aEach patient may have multiple factors, which makes the sum larger than 100%. ^bAir pollution is based on the address of the patients and the official air quality index (AQI).

Abbreviations: NBS, nebulized budesonide; SCS, systemic corticosteroid (oral/intravenous); SD, standard deviation.

hospitalization expenses of all groups, whereas expenses were lowest for the NBS maintenance/reduction group. No between-group differences were seen in improvement in arterial O₂, CO₂, or pH, or in the incidence of new-onset pneumonia.

Stratified Analysis By Baseline PaCO₂

When the four groups were stratified by baseline PaCO₂ (PaCO₂ ≤ 50 mmHg and PaCO₂ > 50 mmHg), between-group differences were seen in mortality in both high and low PaCO₂ groups and in intubation rates in the high PaCO₂ group (Table 3). The SCS escalation group

had a higher mortality rate in those with both low and high baseline PaCO₂. In those with high baseline PaCO₂, the SCS escalation group had the highest rate of intubation and the NBS maintenance/reduction group the lowest (Table 3).

Discussion

In the current post-hoc analysis of a subpopulation from a large, multicenter, non-interventional study of corticosteroid use to treat AECOPD in China,¹⁴ initial use of NBS or SCS for AECOPD generally resulted in similar outcomes and improvements in FEV₁, PaO₂, SaO₂, and PaCO₂.

Table 2 Clinical Outcomes Of NBS Or SCS By Intravenous Injection As Initial Treatment (Grouped By Further Treatment)

	Dose-Escalation Group (NBS Initial)	Dose Maintenance Or Reduction Group (NBS Initial)	Dose Maintenance Or Escalation Group (SCS Initial)	Dose-Reduction Group (SCS Initial)	P-Value
	(N=756)	(N=1443)	(N=404)	(N=518)	
	Mean ± SD				
Length of hospital stay (days)	13.9±7.8	11.7±5.8	11.3±4.9	13.3±5.4	<0.001
Improvement of FEV ₁ (%)	-8.4±44.4	12.0±12.2	7.5±14.1	4.7±10.4	<0.001
Improvement of PaO ₂ (mmHg)	7.5±34.1	5.1±29.3	6.1±40.8	2.3±48.5	0.24
Improvement of PaCO ₂ (mmHg)	-3.5±15.1	-4.3±13.2	-5.9±16.5	-5.1±17.8	0.53
Improvement of SaO ₂	3.5±9.0	3.5±10.8	3.7±13.2	2.9±10.2	0.43
Improvement of pH	0.0±0.1	0.0±0.1	0.0±0.1	0.0±0.1	0.74
Hospitalization expenses	19,004.3±18,522.9	13,582.7±11,680.1	15,154.0±10,625.2	15,856.7±12,616.3	<0.0001
	N (%)				
Intubation rate	25 (3.3%)	26 (1.8%)	13 (3.2%)	13 (2.5%)	<0.001
Mortality	14 (1.9%)	10 (0.7%)	11 (2.7%)	6 (1.2%)	<0.001
Rate of new-onset pneumonia	25 (3.3%)	17 (1.2%)	11 (2.7%)	15 (2.9%)	0.30

Notes: P-value is adjusted by site. The expenses represent all treatment costs during the entire treatment period, including (but not limited to) medications, equipment, bed costs, and care costs. Currency value is RMB.

Abbreviation: SD, standard deviation.

Table 3 Clinical Outcomes Of NBS Or SCS By Intravenous Injection As Initial Treatment (Grouped By Further Treatment), Stratified By PaCO₂

		Dose-Escalation Group (NBS Initial)	Dose Maintenance Or Reduction Group (NBS Initial)	Dose Maintenance Or Escalation Group (SCS Initial)	Dose-Reduction Group (SCS Initial)	P-Value
		(N=756)	(N=1443)	(N=404)	(N=518)	
PaCO ₂ ≤ 50 (mmHg)	Intubation rate	7 (0.9%)	10 (0.7%)	2 (0.5%)	3 (0.6%)	0.37
	Mortality	7 (0.9%)	6 (0.4%)	5 (1.2%)	2 (0.4%)	<0.001
	Rate of new-onset pneumonia	13 (1.7%)	10 (0.7%)	8 (2.0%)	10 (1.9%)	0.19
PaCO ₂ > 50 (mmHg)	Intubation rate	17 (2.2%)	16 (1.1%)	11 (2.7%)	10 (1.9%)	0.001
	Mortality	7 (0.9%)	3 (0.2%)	6 (1.5%)	4 (0.8%)	0.005
	Rate of new-onset pneumonia	10 (1.3%)	5 (0.3%)	3 (0.7%)	5 (1.0%)	0.81

Note: P-value is adjusted by site.

In previous comparisons of the effectiveness of NBS and SCS in the treatment of AECOPD, the two corticosteroid delivery methods have been reported to be more effective than placebo (that is, standard but non-corticosteroid treatment),^{10–12} and to cause similar improvements in FEV₁^{2,10–13} and pH.² In a meta-analysis of five studies, NBS was reported to be non-inferior to SCS.¹⁵ Two studies reported that the increase in PaO₂ was significantly greater with SCS treatment^{2,12} and two reported hyperglycemia

with SCS, but not NBS, treatment.^{19,12} One study reported decreased serum concentrations of inflammatory markers with both NBS and SCS treatment,¹³ but this study included only AECOPD patients who were also suffering from a bacterial infection, and so the decrease in inflammatory mediators was very likely due to antibiotic treatment rather than corticosteroid action. These previous studies were mostly small, with narrowly controlled subject eligibility. Our study results of initial NBS and SCS treatment as used

in clinical practice extend these previous results. We also evaluated the effects of later dose escalation or reduction and of initial PaCO₂ and found these parameters to influence NBS and SCS outcomes. In particular, lower initial PaCO₂ might allow for selection of appropriate patients for initial NBS treatment, but additional controlled studies are needed to better define those most likely to benefit from such treatment.

Our results also showed that, for both NBS and SCS initial treatment, the intubation and mortality rates of the escalation groups were high and similar, with the highest initial hospital cost in the NBS dose-escalation group. Although the use of NBS cannot completely replace the use of SCS for AECOPD patients, the results suggest that certain patients can be considered for NBS therapy during AECOPD. In addition, some patients can be considered for SCS treatment at the outset, and then assessed as to whether a further combination therapy is needed.

Although initial SCS treatment was associated with a shorter duration of AECOPD than initial NBS treatment in the dose-reduction group (14.5 vs. 17.6 days), the difference was not significant ($p=0.33$). In contrast, those in the dose-reduction group receiving initial NBS treatment indeed had shorter length of hospital stays than those receiving initial SCS treatment (11.7 vs. 13.3 days, $p<0.001$). However, the dose-escalation group showed different and interesting results. Although the difference was not significant ($p=0.33$, [Table 1](#)), initial SCS treatment was associated with a shorter duration of AECOPD than initial NBS treatment in the dose-escalation group. Similarly, results in [Table 2](#) showed shorter length of hospital stays in the initial SCS group than in the initial NBS group (11.3 vs. 13.9 days, $p<0.001$). Accordingly, SCS may be slightly preferable to NBS in sicker patients (the dose-escalation group). However, when the dose was reduced (dose-reduction group), NBS treatment performed better and can be considered a better option in the future. The matter warrants further investigation.

In China, it is a routine practice for hospitalized AECOPD patients to be treated with antibiotics to reduce the incidence of pneumonia (97% of the patients in the current study). This practice may be the main reason why the incidence of pneumonia was not significantly different between groups. However, there was a trend for a lower incidence of pneumonia in the NBS-initial/dose-reduction group.

Limitations of the study are its retrospective and post-hoc nature. For example, data availability was limited by the objective of the primary study, and information on

comorbidities and the use of other drugs were not included in this analysis. Use of antibiotics was not a limiting factor, because 97% of the patients received such therapy, in accordance with China guidelines for the treatment of patients with COPD. Other initial drug selection was related to exacerbation severity at the time the patients were hospitalized, but the only such information available were test results such as PaO₂ and PaCO₂, and these, by themselves, are not sufficient for a complete description of the initial severity of the exacerbation. An example of the insufficiency of the available data is that, although overall improvement in FEV₁ was similar in the NBS and SCS groups, FEV₁ worsened in the NBS escalation group and improved in the NBS maintenance/reduction group. This anomaly probably reflects the initial seriousness of the AECOPD. Another probable effect of the underlying initial clinical condition was that the SCS escalation group had a higher mortality rate than the other three groups and that both dose-escalation groups had a higher intubation incidence than the dose-reduction groups when initial PaCO₂ was high. Inclusion of relevant clinical symptoms might have clarified these results.

Conclusion

In summary, these results suggest that, in current clinical practice in China, NBS can be used for initial treatment of AECOPD in certain patients. A lower initial PaCO₂ may allow for the selection of appropriate patients for such treatment, but further studies are needed to better define those most likely to benefit from NBS therapy.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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