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N-acetylcysteine in patients with COPD exacerbations associated with increased sputum

Zeynep Ayfer Aytemur · Aysegul Baysak · Ozer Ozdemir · Timur Köse · Abdullah Sayiner

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Summary
Background N-acetylcysteine (NAC) has been shown not to alter the clinical outcome in chronic obstructive pulmonary disease (COPD) exacerbations. However, NAC may improve symptoms through its mucolytic effect in the subgroup of patients with increased sputum production. The aims of this study were to determine whether NAC improves symptoms and pulmonary function in patients with COPD exacerbation and increased sputum production.

Methods This was a placebo-controlled study, where patients with severe COPD and increased sputum production, who were hospitalized for an exacerbation, were included. They were randomized to receive either NAC 200 mg tid or placebo in addition to the usual treatment.

Results Forty-two patients were included and were equally distributed to NAC and placebo groups. The symptoms, namely, ease of sputum production and dyspnea at rest and on exertion significantly improved in both groups; but there was no difference in improvement between NAC and placebo groups ($p=0.96$, 0.62, 0.31, respectively). Similarly, forced expiratory volume-one second (FEV1) and PaO2 levels improved significantly in NAC (964 ± 599–1239 ± 543 ml, $p<0.001$, and 57.5 ± 14.5–70.5 ± 16.0 mmHg, $p<0.001$, respectively) and placebo groups (981 ± 514–1180 ± 535 ml, $p<0.001$ and 57.9 ± 14.3–68.7 ± 19.0 mmHg, $p<0.001$, respectively), without any difference between the two groups ($p=0.52$ and 0.57). There was no difference in the number of exacerbations during the 6-month follow-up period.

Conclusion NAC does not have any beneficial effect on clinical outcomes in patients with severe COPD exacerbation associated with increased and/or viscous mucus production.

Keywords Chronic obstructive pulmonary disease · Exacerbation · Treatment · N-Acetylcysteine · Mucolytic

Prof. A. Sayiner (✉)
Department of Chest Diseases, Ege University Faculty of Medicine, Izmir, Turkey
e-mail: zeynep.ayfer@gmail.com

Z. A. Aytemur
Department of Chest Diseases, Inonu University Faculty of Medicine,
Malatya, Turkey

A. Baysak
Department of Chest Diseases, Izmir University Faculty of Medicine,
Izmir, Turkey

O. Ozdemir
Siverek State Hospital,
Sanliurfa, Turkey

T. Köse
Department of Medical Informatics and Biostatistics,
Ege University Faculty of Medicine,
Izmir, Turkey

N-Acetylcystein bei Patienten mit Exazerbation einer COPD mit erhöhter Sputumproduktion

Zusammenfassung
Grundlagen Es ist gezeigt worden, dass N-acetylcystein (NAC) das klinische Outcome einer COPD Exazerbation nicht verändert. NAC könnte aber die Symptome einer COPD durch seine schleimlösende Wirkung in einer Untergruppe von Patienten mit vermehrter Sputumproduktion bessern. Ziel dieser Studie war es zu prüfen, ob NAC die Symptome und die Lungenfunktion bei Patienten mit einer Exazerbation einer COPD mit vermehrter Sputumproduktion bessern kann.

Methodik In diese Placebo-kontrollierte Studie wurden Patienten mit schwerer COPD und vermehrter Sputumproduktion, die wegen einer Exazerbation hospitalisiert

worden waren, aufgenommen. Randomisiert erhielten sie zusätzlich zu ihrer Behandlung entweder 200 mg NAC 3x täglich oder Placebo.

Ergebnisse Zweiundvierzig Patienten wurden in die Studie aufgenommen. Sie erhielten – gleich verteilt – NAC oder Placebo. Die Symptome, nämlich die Leichtigkeit der Sputumproduktion und die Atemnot in Ruhe und bei Belastung besserten sich in beiden Gruppen signifikant. Allerdings gab es zwischen den beiden Gruppen (NAC oder Placebo) keinen Unterschied in der Besserung ($p = 0{,}96$, 0,62, 0,31). Ebenso besserten sich die FEV1 und die PAO2 Werte in der NAC (964 ± 599 zu 1239 ± 543 ml, $p < 0{,}001$, und 57,5 ± 14,5 zu 70,5 ± 16,0 mmHg, $p < 0{,}001$) und in der Placebo Gruppe (981 ± 514 zu 1180 ± 535 ml, $p < 0{,}001$ und 57.9 ± 14.3 zu 68.7 ± 19.0 mmHg, $p < 0{,}001$) ohne jeglichen Unterschied innerhalb der beiden Gruppen ($p = 0{,}52$ und 0,57). Es gab auch keinen Unterschied in der Anzahl der Exazerbationen während der 6-monatigen Kontrollperiode.

Schlussfolgerung NAC hat keine günstige Wirkung auf das klinische Outcome bei Patienten mit Exazerbation einer schweren COPD mit gesteigerter und/oder visköser Schleimproduktion.

Schlüsselwörter Chronisch obstruktive Lungenerkrankung · Exazerbation · Behandlung · N-Acetylcystein · Schleimlösend

Introduction

Difficulty in expectoration is one of the cardinal symptoms in chronic obstructive pulmonary disease (COPD) and usually gets worse in exacerbations when the sputum volume increases. Sputum production is an independent factor affecting quality of life [1]. Besides, increased sputum production has been reported to be associated with more respiratory symptoms and worse airflow obstruction in severe COPD [2]. Thus, any intervention that makes it easier for the patient to clear his secretions may have a positive impact on how the patient feels.

N-acetylcysteine (NAC) has been shown to have mucolytic and antioxidant properties [3, 4] and to reduce the frequency of exacerbations when used in the stable period [5]. In some parts of the world, it is frequently used in COPD exacerbations with the intention to help patients clear their secretions more easily and to benefit from its antioxidant properties.

One randomized controlled trial performed in patients with COPD exacerbations showed that a 7-day treatment had no effect on the level of dyspnea, forced expiratory volume-one second (FEV1), and SaO2 and did not shorten the length of hospital stay [6]. The study, however, included all COPD patients admitted to the hospital for exacerbation.

We hypothesized that, during exacerbations NAC may only exert its beneficial mucolytic effect in the subgroup of patients with increased sputum production. Thus, this study was planned with the aim to determine whether the subgroup of patients with severe COPD exacerbation and with increased sputum volume may significantly benefit from the addition of NAC to standard treatment with inhaled bronchodilators.

Patients and methods

This was a single-center, prospective, double-blind, placebo-controlled study that involved patients with COPD exacerbation. The study was reviewed and approved by the Ethics Committee of Ege University and performed in accordance with the ethical standards laid down by the Declaration of Helsinki.

Study population

Patients were included in the study if they had a spirometrically confirmed prior diagnosis of COPD, had a smoking history of at least 20 pack-years, were hospitalized for their current exacerbation, and reported increased sputum production of more than 50 ml per day. This volume was empirically selected because it possibly represents production of sputum throughout the day (not only in the morning hours) and is easy to describe by the average patient since it is roughly the volume of an ordinary Turkish coffee cup.

The exclusion criteria were the presence of a prior diagnosis of asthma or bronchiectasis, radiographic evidence of pneumonia, and use of any mucolytic drug during the preceding week. All participants gave written informed consent.

Study medications

All patients received standard treatment including inhaled beta-agonists and anticholinergics, systemic steroids and antibiotics, as determined by their physicians. At admission to the ward, the patients were randomized to receive either NAC capsules 200 mg tid or identical-looking placebo capsules for 30 days. These were kindly provided by Bilim Pharmaceuticals, Istanbul, Turkey. The company had no other involvement in the design, execution or interpretation of the study. All study medications were prepackaged and numbered according to a randomization list and all the parties were blinded to the study medication the patients received.

Study endpoints

The primary endpoints were the degree of improvement in symptoms, namely sputum production, shortness of breath, and wheeze as assessed at admission, on days 1 and 3 and at the time of discharge or on day 10, whichever came first. According to the protocol, the patients remained in the hospital for at least 7 days, for

the symptoms to be monitored. Thereafter, the time of discharge was left at the discretion of the attending physician. The symptoms were scored on a 7-point scale, where 1 signified "the worst possible state/symptom very significantly affecting daily life" and 7 signified "the best possible state/patient did not report any symptom". This scale was previously used in a similar trial for shortness of breath [6]. This also allowed the patients to more easily score their sputum production and wheezing using the same scale.

The secondary endpoints were the improvement in arterial blood gases and in FEV1 level, as assessed at admission and at the time of discharge or day 7. The final endpoint was recurrence of exacerbation after discharge during the 6-month follow-up.

Pulmonary function tests were performed at bedside using a handheld spirometer (Micromedical Microplus, Kent, UK) according to the recommendations issued by American Thoracic Society [7] and the reference values were those recommended by the European Respiratory Society [8].

Statistical analysis

We made a power calculation based on two similar studies on the effects of theophylline and NAC in COPD exacerbations [6, 9]. In the theophylline study [9], the average improvement in Likert score for breathlessness was 1.95 with theophylline and 1.05 with placebo. Similar to the previous NAC study [6], we assumed the study population would have a similar distribution of symptom scores for breathlessness. Thus, we estimated that 50 patients would give 88 % power to detect an improvement in symptoms at a 5 % level of significance.

Fisher's exact test was performed for comparisons of categorical variables between study groups. Numerical variables were compared between the NAC and placebo groups using the Student's t-testest for independent samples. All tests were performed at $\alpha = 0.05$ significance level. IBM-SPSS (version 19.0 for Windows) statistical software package was used for all statistical analyses.

Results

Forty-two patients were included in the study and were randomized into the NAC group ($n = 20$) and placebo group ($n = 22$). The target population of 50 patients could not be reached within the expiration period of the study drugs.

One patient from NAC group and three patients from the placebo group, who worsened during the first 3 days of the treatment period, were admitted to the intensive care unit and were intubated. Two of the three patients in the control group died. The data from these patients were excluded from analysis. Thus, 19 patients from each group completed the study. The two groups had similar demographic and clinical characteristics (Table 1).

Table 1 Baseline characteristics of the study and placebo groups

	NAC group ($n = 19$)	Placebo group ($n = 19$)	p value
Mean age (years)	68.6 ± 7.5	69.4 ± 9.9	0.869
Gender (M/F)	17/2	18/1	1.00
Duration of COPD (years)	19.0 ± 14.9	11.4 ± 7.5	0.057
Mean baseline FEV1 level (ml)	1087 ± 365	1144 ± 655	0.751
Mean baseline FEV1 level (pred%)	39,3 % ± 14.6	45.5 % ± 25.5	0.438
Mean baseline PaO_2 level (mmHg)	58.7 ± 15.4	56.5 ± 12.6	0.629
Mean baseline $PaCO_2$ level (mmHg)	42.3 ± 12.5	47.4 ± 13.9	0.246

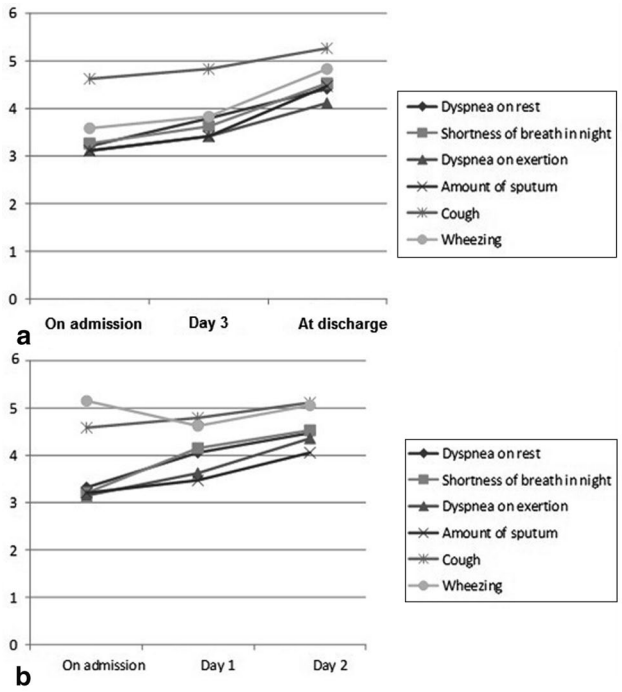

Fig. 1 Symptom scores at admission, day 3 and at discharge in the NAC (**a**) and placebo groups (**b**)

All patients received systemic steroids at similar doses (40 mg qd) and similar nebulized bronchodilator therapy (ipratropium 500 mcg and salbutamol 2.5 mg q6 h). Fifteen and 16 patients from the NAC and placebo groups, respectively, were given antibiotics.

All measurements were obtained on admission and at discharge. The length of hospital stay was similar in the NAC and control groups (10.5 ± 3.8 and 9.8 ± 3.0 days, respectively, $p = 0.52$).

The primary endpoints: All symptoms improved in both groups (Figs. 1a and 1b), but there was no difference in the areas under the symptom score–time curves between the two groups (Table 2).

The secondary endpoints: There were significant improvements in FEV1 levels at discharge in both groups (Table 3). Although this improvement tended to be

Table 2 Areas under the symptom score–time curves for the two groups

	NAC group	Placebo group	*p*
Dyspnea at rest	31.9±4.8	30.9±7.2	0.616
Dyspnea at night	32.6±5.4	31.6±7.1	0.637
Dyspnea on exertion	30.6±5.7	28.4±7.4	0.309
Ease of sputum production	35.7±8.9	35.6±8.5	0.959
Wheeze	29.3±7.1	31.0±8.3	0.496

numerically larger in the NAC group (366.3 ml) compared with the placebo group (201.8 ml), this difference did not reach statistical significance ($p=0.076$). Arterial blood gases were measured at admission and at discharge or on day 7, whichever came first. There was a significant improvement in oxygen saturation and PaO2 levels at discharge in both groups. The level of improvement was similar for the two groups (Table 3).

All patients were followed-up for a period of 6 months for recurrent exacerbations. There was no difference between the two groups with regards to the number of exacerbations, the time to the first exacerbation and the number of hospitalizations for recurrent exacerbations (Table 4).

Discussion

This was a randomized, double-blind, placebo-controlled study aiming to critically examine the effects of NAC treatment during exacerbations of COPD. We found that treatment with NAC did not affect the length of hospital stay, the rate of improvement in symptoms, FEV1, oxygen saturation and PaO2 levels at discharge, the number of exacerbations, the time to the first exacerbation, and the number of hospitalizations for recurrent exacerbations during the 6-month follow-up.

Approximately one-third of patients with severe COPD describe severe sputum symptoms on a daily basis, despite aggressive medical therapy with long acting bronchodilators and corticosteroids [2]. Chronic mucus hypersecretion is significantly associated with an increased risk of respiratory infection, accelerated lung function decline, and hospitalization for COPD patients [10, 11]. Patients with the chronic bronchitic phenotype more frequently report wheezing and nocturnal awakenings secondary to cough and dyspnea [12]. Thus, any intervention that would reduce mucus production or that would facilitate its clearance, leading to a decreased mucus load in the airways, would be expected to be associated with improved clinical outcomes.

Table 4 The exacerbations during the 6-month follow-up period

	NAC group	Placebo group	*p* value
Number of AECOPD (mean)	1.1±1.3	1.0±1.4	0.788
Time to AECOPD (days)	50.4±66.2	22.7±27.6	0.347
Number of hospital admissions at follow-up	0.9±1.1	0.6±0.9	0.424
Time to hospital admission (days)	45.6±67.2	24.6±41.5	0.373

AECOPD Acute exacerbations of chronic obstructive cardiopulmonary disease

NAC is known to have antioxidant and mucolytic properties. Several studies have been performed to determine the effectiveness of its long-term use in the stable period. A meta-analysis indicated that NAC significantly reduced the odds of experiencing one or more exacerbations over the treatment period in patients with COPD [13]. Similarly, a subsequent review concluded that mucoactive drugs may deserve consideration in the long-term treatment of COPD [14]. In the largest randomized, placebo-controlled study that was done in 50 centers, 523 patients with COPD were randomly assigned to 600 mg daily NAC or placebo and they were followed up for 3 years. This study showed that NAC did not affect the rate of decline in FEV1 or forced vital capacity (FVC), exacerbation rate, or health status in the overall population. However, there was a significant decrease in the frequency of exacerbations in the subgroup who did not receive inhaled steroids [5]. Another large study with carbocisteine also demonstrated a significant reduction in the frequency of exacerbations and an improvement in health-related quality of life [15].

There is little data on the effects of the use of NAC during exacerbations on clinical outcomes. In one study, Zuin R et al. investigated the efficacy and tolerability of high-dose NAC in the treatment of patients with exacerbations of COPD. This study showed that treatment with NAC at doses of 600 and 1200 mg/day was associated with a significantly higher proportion of patients achieving normal C-reactive protein levels compared with placebo

Table 3 FEV1 levels and arterial blood gases at admission and at discharge

	NAC group			Placebo group		
	Admission	Discharge	*P*	Admission	Discharge	*p*
FEV1 (ml)	964±599	1239±543	0.001[a]	981±514	1180±535	0.007[a]
pH	7.42±0.07	7.44±0.05	0.444	7.42±0.03	7.41±0.04	0.916
PaO_2 (mmHg)	57.5±15.8	70.5±15.0	0.001[a]	57.9±17.9	68.7±12.4	0.001[a]
$PaCO_2$ (mmHg)	42.3±13.2	43.5±9.1	0.583	47.4±16.9	44.5±5.3	0.753
SaO_2 (%)	86.2±15.2	92.9±4.5	0.009[a]	87.0±10.3	92.6±4.5	0.003[a]

[a]There was no difference in the rate of improvement in FEV1, PaO2 and SaO2 levels between the two groups ($p=0.076$, $p=0.777$ and $p=0.979$, respectively)

and the higher-dose was more efficacious than the lower dose in reducing IL-8 levels and improving the difficulty of expectoration. The two active regimens had similar beneficial effects on lung function, cough intensity, cough frequency, and lung auscultation findings [16].

Another placebo-controlled study examined the effects of NAC at a dose of 600 mg/day in the treatment of COPD exacerbations [6]. The treatment was continued for 7 days or until discharge. There was no effect of NAC on the levels of breathlessness, FEV1, SaO2, and length of hospital stay.

Because of the conflicting findings from these two previous studies, the present study was undertaken to investigate whether a subgroup of patients with increased sputum production would benefit from a mucolytic drug. Similarly to the study by Black et al., no beneficial effect was demonstrated both during the hospitalization period and at follow-up.

This study had several limitations. First, we were not able to reach the targeted number of patients because we were limited with the expiration date of the study drugs and we did not have any chance for the production of a new batch of drugs. However, we were able to include all consecutive patients meeting the inclusion criteria. The findings are quite consistent and there does not seem to be a signal which implies the results could be different if a larger group of patients were studied.

Second, the cutoff level of 50 ml to define mucus hypersecretion may be considered to be more than usual, but it defines a patient subgroup with the highest likelihood of benefiting from the drug. This, in fact, was the main reason for the limited number of patients that could be included in the study.

Third, it can be argued that the sputum volume was estimated subjectively by the patients and that there would be a possibility of over or underestimation. However, these were patients with a long history of COPD, who were used to monitoring their symptoms and to being questioned about their sputum production each time they visited their doctor. This question is frequently posed using scales from their daily life, e.g., a spoon, a Turkish coffee cup, or a Turkish tea glass.

Fourth, the effects of different doses of NAC were not evaluated. The current dose was chosen because this is the dose at which the drug is licensed and is marketed in our country for use in acute exacerbations in COPD. This study, thus, aimed to evaluate the efficacy of the current practice. Besides, in the largest and best-designed study of NAC during the stable period, where there was a reduction in the frequency of exacerbations in patients not receiving inhaled steroids, the dose was again 600 mg qd [5]. Yet, it may be worthwhile to examine the effect of higher doses, as both NAC and carbocisteine have shown to better improve clinical outcomes at high doses [15, 16].

Apart from the dose, another reason for the failure to find a significant effect on the clinical outcomes may be that all patients also received systemic steroids during their hospitalization. As was observed in the BRONCUS Trial, NAC does not seem to exert any additional beneficial effect in patients who receive concomitant steroids. In view of the better safety profile of NAC compared with systemic steroids, it may be worthwhile to look at its efficacy in mild exacerbations that do not necessitate treatment with steroids.

This study can also be criticized for its protocol which required that the patients be hospitalized for at least 7 days. We thus intended to obtain uniform measurements to better evaluate the drug efficacy. This may have altered the reported lengths of stay, but only seven (18.4 %) of the patients were discharged on day 7. Besides, a recent survey has shown that the average length of hospital stay for COPD exacerbations in our institution is 9.4 days, similar to the findings in this study (Sayiner A. unpublished data). Thus, it does not seem very likely that the protocol requirement for the length of hospital stay may have altered the results.

Another criticism could be that the follow-up period was limited to 6 months. We do not think a longer period would be relevant as this study only aimed to determine the effects of NAC treatment given during an exacerbation and the following month. This relatively short course would not be expected to affect recurrences beyond 6 months.

In conclusion, we found that NAC given at a daily dose of 600 mg to patients with COPD exacerbations and with a high volume of sputum production did not affect symptoms, pulmonary function, length of hospital stay, and exacerbation rate during the follow-up period. These findings should be interpreted with caution as the targeted number of participants was not attained. The data are still relevant in that mucolytics are frequently prescribed for exacerbations. Thus, together with the findings of Black PN et al., we now have further evidence that argue against the use of mucolytics during exacerbations.

Conflict of interest

The authors declare that there are no actual or potential conflicts of interest in relation to this article.

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