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Effects of N-Acetylcysteine on Asthma Exacerbation

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ABSTRACT

Airway mucus hypersecretion and increased oxidative stress are clinical and pathophysiological features of asthma exacerbation. We studied effects of N-acetylcysteine (NAC) as a mucolytic and antioxidant agent in asthma exacerbation.

In this randomized, single-blinded, placebo-controlled study 50 patients (17 male, 33 female, mean age 48.94±13.68) with asthma exacerbation were randomized to receive either oral 600 mg b.d. N-acetylcystiene or placebo in addition to standard treatment during 5 days hospitalization. Daily measurements of wheezing, dyspnea, cough, sputum, expectoration, night sleep scores and morning PEFR were performed.

There was no significant difference in wheezing score between patients assigned NAC and those assigned placebo in day 5(0.84[SD 0.94] VS 0.87[SD 0.79]) and also in cough score (0.72[SD 0.84] VS 0.79[SD 0.97]), dyspnea score (0.84[SD 1.06] VS 0.91[SD 1.01]), sputum score(0.79[SD 0.83] VS 0.62[SD 0.71]), expectoration score(0.79[SD 0.97] VS 0.83[SD 1.09]), night sleep score(1[SD 1.17] VS 0.67[SD 0.98] and morning PEFR (256[SD 96.36] VS 282[SD 98.86]).

We concluded that addition of N-acetylcysteine to usual asthma medication has no significant effect in treatment of asthma exacerbation.

Key words: Antioxidant; Asthma; Mucus Hypersecretion; Mucolytic; N-Acetylcysteine

INTRODUCTION

Airway mucus overproduction and mucus plugging with airflow obstruction are pathophysiologic features of asthma and contribute not only to airway hyperresponsivness but also to morbidity and mortality of this disease.[1-5] Difficulty in clearing of airway mucus has been demonstrated in most asthmatic patients.[6]

On the other hand oxidant/antioxidant imbalance have been shown in asthma[7-9] as a consequence of chronic airway inflammation. [10] The oxidants can also amplify inflammation in asthmatic airways with many pathophsiological effects including mucus hypersecretion.[11] Asthma severity and acute exacerbation of asthma are associated with increased oxidative sress.[1,12]

N-acetylcysteine (NAC) breaks disulfate bonds and is one of the most effective agents for reducing sputum

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viscosity. [13-15] NAC as a mucolytic agent may be able to produce a modest improvement in symptoms and lung function by altering the mucus secretion and its physical properties in asthma.[16]

NAC also is a thiol antioxidant which has the potential to interact either directly with oxidant or indirectly by replenishing depleted glutathione stores. NAC can block the release of inflammatory mediators from epithelial cells and macrophages, inhibit adhesion molecules, and also inhibit neutrophil chemotaxis, activation and aggregation.[17-19] The antioxidant protective effect of NAC can attenuate inflammation in experimental asthma.[20]

We studied effects of N-acetylcysteine as a mucolytic and antioxidant agent in asthma exacerbation in order to determine its benefit in treatment of asthma.

MATERIALS AND METHODS

From March 2006 to October 2008, fifty consecutive patients with asthma exacerbation who were admitted to the pulmonary ward of Beheshti teaching hospital, Babol university of medical sciences, were enrolled in this randomized, single-blinded, placebo-controlled study. The subjects were allocated to two groups using a 1:1 ratio randomization table. Patients had well-defined history of physician-diagnosed asthma. Patients with a history of smoking, COPD, bronchiectasis, and chronic bronchitis were excluded.

The subjects were randomized to receive either oral N-acetylcysteine 600 mg b.d. or placebo in addition to usual medication within 24 hour of admission after initial stabilization by administering short acting $ß_2$ agonist and/or anticholinergic bronchodilators, and parenteral corticosteroid. During hospitalization all subjects were received usual asthma medication including parenteral corticosteroid, short-acting and then long-acting $ß_2$ agonist, inhaled corticosteroids with the same doses and where appropriate macrolid antibiotics was necessary.

In all patients daily assessment including determining dyspnea, wheezing, cough, sputum, ability of expectoration, quality of night sleep scores, based on asthma daily symptoms severity assessment diary[21], and morning PEFR measurements, using a hand-hold peak flow meter, were performed during first 5 days of hospitalization. (Table 1) Of course, we added two variables, sputum and ability of expectoration, to this symptoms assessment sheet to evaluate clinically the effect of NAC on sputum quality. For measuring of PEFR, patients instructed to perform maneuver three times and the highest of the three measurements was recorded.

Research ethics board of the Babol medical university approved the study and permission was obtained from the patients.

Descriptive analyses were made using a statistical software package (SPSS, version15). The data were presented as the mean±SD unless otherwise indicated. $P<0.05$ was considered to be statistically significant. Statistical comparison among the variables and two groups were made using Paired t-test and Mann-Whitney U test, respectively.

Table 1. Daily variables scoring based on asthma daily symptoms severity assessment

Score / Variable	0	1	2	3
Wheezing	None	Some	Medium	Severe
Cough	None	Occasional	Frequent	Continuous
Sleep	Fine	Slight wheeze or Cough	Awake 2-4 times by wheeze or cough	Awake most of the time
Dyspnea	No dyspnea	DOE with moderate exercise	DOE with minimal exercise	Dyspnea at rest
Sputum	No Sputum	Some	Frequent	Continuous
Expectoration	Expectorate with no difficultly	Expectorate with Some difficultly	Difficult Expectoration	Cannot Expectorate

Table 2. Patients characteristics of two groups

Characteristics	NAC N=25	Placebo N=25	P value
Sex(No.)			
Male	10	7	
Female	15	18	
Age(yr)	50±15.74	47.8±12.06	0.235
Asthma duration(yr)	8.08±7.12	7.96±8.53	0.746
Duration of exacerbation(day)	6.04±4.16	7.54±6.35	0.086
First day morning PEFR(L/min)	192.17±91.74	141.42±75.64	0.053
Medication used during hospitalization(No.)			
Inhaled corticosteroid	25	25	
Systemic corticosteroid	25	25	
Inhaled ß$_2$ agonist	25	25	
Macrolide antibiotics	15	12	

Values are given as No., mean±SD. p<0.05 is significant.

RESULTS

Patients characteristics are presented in table 2. The mean±SD age was 48.94±13.68 years among the patients of whom 34% were men and 66% were women. One patient in placebo group could not complete the study because of respiratory failure and mechanical ventilation in day 3. Comparison of variables between two groups are summarized in Table 3. No significant differences were found in mean±SD of dyspnea, wheezing, cough, sputum, expectoration, night sleep quality scores and morning PEFR in day 1.

In day 5 the mean±SD of dyspnea score between patients assigned NAC and those assigned placebo was 0.84±1.06 VS 0.91±1.01 (p=0.798) and also of wheezing score 0.84±0.94 VS 0.87±0.79 (p=0.889), cough score 0.72±0.84 VS 0.79±0.97 (p=0.784), sputum score 0.79±0.83 VS 0.62±0.71 (p=0.460), expectoration score 0.79±0.97 VS 0.83±1.09 (p=0.890), night sleep score 1±1.17 VS 0.67±0.98 (p=0.308) and morning PEFR 256±96.36 VS 282±98.86 (p=0.369).We were found no significant differences in mean±SD of these scores in day 5 (Figure 1).

Table 3. Comparison of variables score and morning PEFR between two groups

Variables	First day			Fifth day		
	NAC N=25	Placebo n=25	P value	NAC	Placebo n=25	P value n=24
Dyspnea	2.6±0.81	2.8±0.4	0.279	0.84±1.06	0.91±1.01	0.798
Wheezing	2.64±0.7	2.72±0.73	0.696	0.84±0.94	0.87±0.79	0.889
Cough	2.44±0.76	2.48±0.82	0.860	0.72±0.84	0.79±0.97	0.784
Sputum	2.04±1.23	2±1.11	0.902	0.79±0.83	0.62±0.71	0.460
Expectoration	1.88±1.16	2±1.25	0.728	0.79±0.97	0.83±1.09	0.890
Night sleep	2.45±1.06	2.68±0.62	0.376	0.68±0.98	1±1.17	0.308
Morning PEFR	192.17±91.74	141.42±75.64	0.053	282±94.86	256.95±96.36	0.369

Data are presented as mean±SD. p<0.05 is significant.

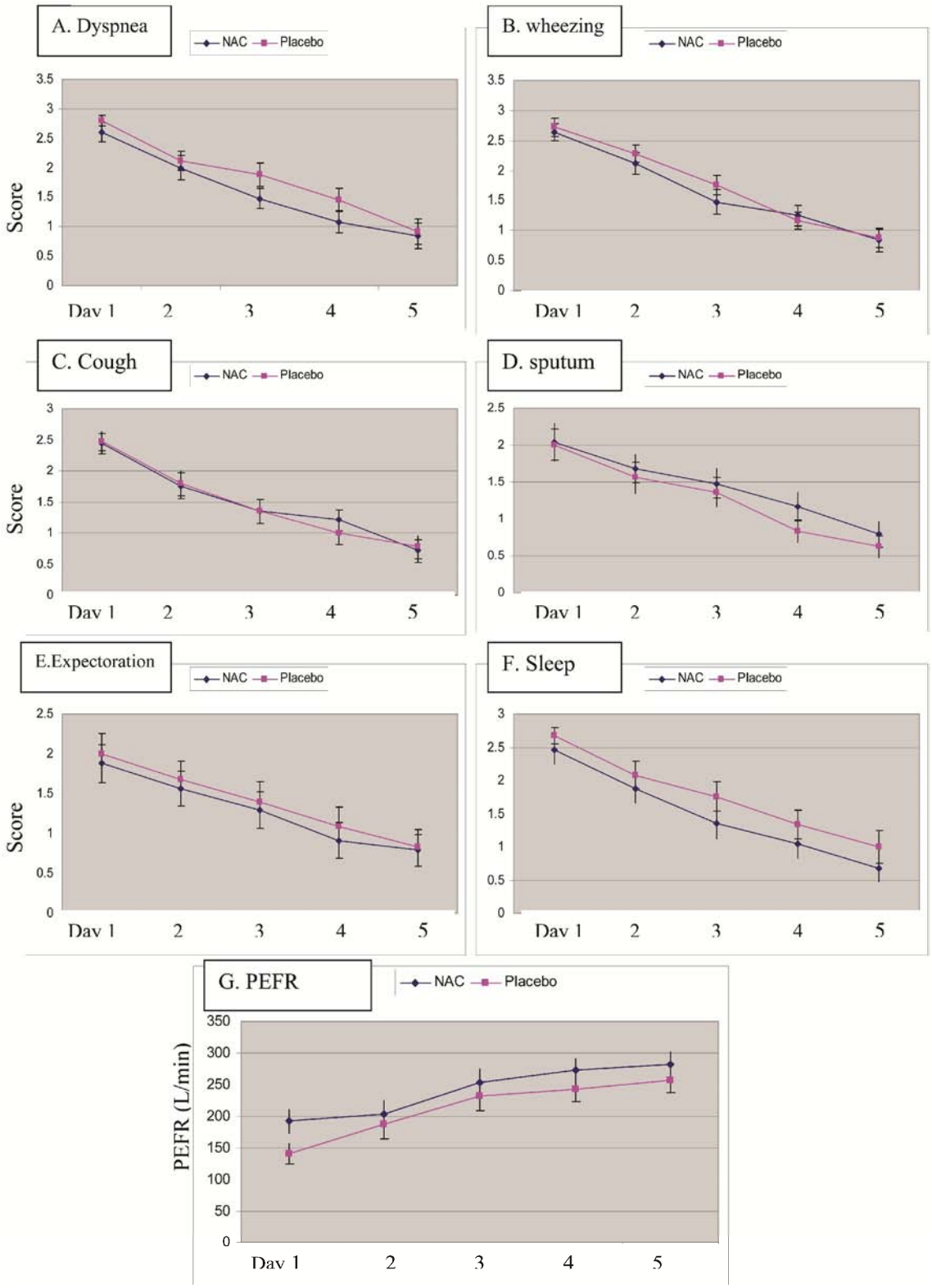

Figure 1. Scores change during 5 days in two groups

DISCUSSION

Although airway mucus overproduction and hypersecretion are clinical and pathophysiologic features of patients with asthma exacerbation, we found no significant effect of NAC on outcome in acute asthma exacerbation. This study has shown that NAC as a mucolytic agent has no effect on sputum and ability of expectoration in comparison to placebo. Other clinical variables including dyspnea, wheezing, cough, night sleep quality and morning PEFR were not affected significantly by using of NAC. although the importance of mucus hypersecretion and mucus plugging to airflow limitation and to morbidity and mortality in asthma are confirmed, but mucoactive drugs are still not accepted in asthma management guidelines in part because lack of well designed clinical trials[22,23] and probably these agents unable to affect significantly on airway obstruction related to mucus.[24]

Conventional therapies for mucus hypersecretion in patients with airway disease like asthma, COPD and cystic fibrosis include beta 2-adrenoceptor agonists, anticholinergics, glucocorticosteroids, mucolytics and macrolide antibiotics. The efficacy of these drugs in inhibiting airway mucus hypersecretion is variable with effect in some airway disease and no effect or less effective at all in others. Therefore, new therapeutic targets are being investigated that focused on inhibiting mucin synthesis and secretion, goblet cell hyperplasia and cholinergic nerve activity. Inhibition of Th2 cytokines (IL-4, IL-9, IL-13) may also be effective in asthma. [25-27] However, the benefits from inhibiting mucus hypersecretion and clinical usefulness of these drugs are still not certain.[27] We should keep in mind that mucin hypersecretion is not only a marker of disease but moving towards being testable as functional components of airway disease processes.[28]

Aylward et al showed oral NAC increased sputum volume, decreased sputum thickness and improved in dyspnea and ease of expectoration scores in patient with chronic bronchitis.[29] The changes in sputum composition has been shown in another study in patients with chronic bronchitis. The lower scores for sputum volume, degree of purulence, thickness of sputum, difficulty in expectoration and severity of cough have been reported by patients who take oral NAC.[30] As far as we know, there is no study of using NAC in asthma exacerbation, but in comparison to effects of NAC on chronic bronchitis, our study showed no significant effects on sputum volume and dyspnea, ease of expectoration and cough scores by NAC at least in short term. Similar finding has been reported in acute exacerbation of COPD by Black et al, with no effect of NAC on outcome of these patients.[31] In a study by Bylin et al the effect of NAC has been investigated in patients with stable symptomatic asthma during 3 weeks. The NAC had no effect on spirometric, lung mechanic, gas exchange variables and also frequency of pulmonary symptoms.[32]

There is increasing evidence of oxidant-antioxidant imbalance in asthma with increased oxidative stress especially during exacerbations. Despite potency of lungs antioxidant system, overproduction of endogenous or exogenous reactive oxygen species and reactive nitrogen species lead to airway inflammation, airway hyperresponsiveness, airway microvascular hyperpermeability and remodeling in animals models and human studies.[33-35] There is good evidence that suggests antioxidant compounds including a novel thiol compound Nacetylcysteine amid (AD4), may have a potential role in the treatment of asthma, especially of asthma exacerbation.[36,37] In has also been shown that NAC as an antioxidative compound reduced chemokine release in human airway smooth muscle cells.[38]

In present study, we found no effect of NAC as an antioxidative agent in modifying clinical recovery of acute asthma exacerbations. The possible reasons of this observation may include 1) appearance of clinical effect of antioxidative property of NAC may need higher doses probably because penetration of NAC into airway still not clear [39]or 2) antioxidative effect of NAC is small when given in addition to corticosteroids as highly effective agents in suppressing inflammation or 3) antioxidant property of NAC may have no clinical importance because this agent has not enough potency for reducing oxidative stress.[40] Of course, we are aware that small sample size and short course of study and also subjective assessment of symptoms are limitations to conclude this results exactly.

Furthermore, Single-blindness of this study also maybe a source of potential bias. Verifying the findings of this study needs a double-blind design in future. Despite these limitation, we believe that the results of this trial support the current concept regarding ineffectiveness of usual mucolytic agents, e.g. NAC, in routine management of asthma exacerbation and the need for introducing new compounds to inhibit airway mucus hypersecretion.

In conclusion, we demonstrated that addition of NAC to usual asthma medication has no significant effect in treatment of asthma exacerbation.

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