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N-Acetylcysteine Improves the Clinical Conditions of Mustard Gas-Exposed Patients with Normal Pulmonary Function Test

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Abstract: Administration of N-acetylcysteine may be effective in diseases caused by oxidative–antioxidative imbalance. We aimed to determine the effect administration for 4 months of N-acetylcysteine (1200 mg daily) on sulfur mustard-induced bronchiolitis obliterans in patients with normal pulmonary function test. In a double-blind clinical trial, 144 patients with bronchiolitis obliterans due to sulfur mustard and bronchiolitis obliterans syndrome class 0, randomly entered to group 1 (n = 72, N-acetylcysteine) and group 2 (n = 72, placebo). The changes in dyspnoea, wake-up dyspnoea, cough and sputum were measured after 4 months using a 'delta value' (i.e. symptom score after 4 months – symptom score before the trial). Spirometric findings were measured at the beginning of the trial, 2 months later and 4 months later. Dyspnoea (delta value: –0.78 (0.61), $P < 0.001$), wake-up dyspnoea (delta value: –0.57 (0.64), $P < 0.001$), and cough (delta value: –0.86 (0.63), $P < 0.001$) improved after 4 months of N-acetylcysteine administration compared to the control group. N-acetylcysteine reduced sputum from 76.9% (n = 40) of cases before the trial to 9.6% (n = 5) of cases after the trial. Spirometric components were significantly improved in N-acetylcysteine group compared to the placebo group: FEV1 ($P < 0.0001$), FVC ($P = 0.014$) and FEV1/FVC ($P = 0.003$). A 4-month trial with 1200 mg oral N-acetylcysteine per day can be used for treating bronchitis, but is also effective in treating bronchiolitis. It also prevents sulfur mustard-induced oxidative stress, and can be used in the treatment of sulfur mustard-induced pulmonary disease.

More than 40,000 people suffer from pulmonary diseases due to sulfur mustard [1]. There is no common consensus about the pathophysiological basis of chronic pulmonary disease caused by mustard gas [2,3], but bronchiolitis obliterans has been proposed as the underlying cause [4–7].

Some studies have shown that sulfur mustard-induced pulmonary disease is a neutrophil and/or lymphocyte dominant disorder (e.g. neutrophil-dominated inflammatory process). Neutrophil dominant disorders, such as chronic obstructive pulmonary disease (COPD), bronchitis, bronchiectasis and emphysema, are characterized by increased inflammation and tissue injuries due to neutrophil-secreted enzymes and cytokines. Among the theories that have tried to explain these disorders, one formulates that neutrophils and lymphocytes secret proteases which themselves produce oxygen species [8].

These patients suffer from respiratory symptoms although a majority of them have normal pulmonary function tests. Patients with sulfur mustard-induced pulmonary disorder often receive bronchodilators, corticosteroids, immunosuppressive agents, antibiotics, mucolytics, long-term oxygen therapy and physiotherapy. But these different treatments are not as effective as predicted and also have known adverse effects [1]. In parallel, these patients do not respond well to bronchodilators due to the non-obstructive nature of their disease. Hence, it is reasonable to look for new drugs and protocols in order to substitute the old ones.

By considering the oxidative–antioxidative imbalance in the pathophysiology of sulfur mustard-induced pulmonary lesions, it is useful to consider antioxidant as a treatment option [7]. N-Acetylcysteine is a mucolytic drug but can improve clinical conditions in COPD [9–11], fibrosing alveolitis [12] and idiopathic pulmonary fibrosis [13] through its antioxidant properties.

N-Acetylcysteine can also alter the inflammatory processes, which are the main cause of disease progression in chronic pulmonary diseases. This alteration is evident in changes in the amount of some cytokines, different gene expression and different pattern of receptor activation [14]. It has been shown that N-acetylcysteine reduces the number of neutrophils in lung injuries in mice exposed to sulfur mustard [15].

We conducted a double-blind, placebo-controlled clinical trial to investigate if administration of N-acetylcysteine over 4 months would ameliorate the clinical conditions of sulfur mustard-exposed patients who have normal pulmonary function tests.

Materials and Methods

Patients. The study was designed as a parallel group trial of 1200 mg daily oral N-acetylcysteine versus placebo. We enrolled 144 patients in this study who were randomly allocated to the placebo or the N-acetylcysteine group with random number table.

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Conflict of interest statement: The authors had conflict of interest because the drugs (Fluimicil) were provided by Zambon Co. Since all the stages of this study were done in a double blind fashion, the conflict of interest did not affect the results.

Each group consisted of 72 patients. Patients were free to leave the study. The trial was approved by the ethical committee of the research centre of chemical injuries, and informed consent was obtained from all patients.

The participants were patients suffering from pulmonary disorders due to previous exposure to a single high dose of sulfur mustard gas during the Iran–Iraq conflict in 1988. They were all from Sardasht, a city in western Iran.

Inclusion criteria were as follows: documented exposure to sulfur mustard; documented diagnosis of chronic pulmonary disease due to mustard gas (histological evidence from previous biopsies) and no history of tuberculosis or resection of one or more lobes of lung. Exclusion criteria were pneumonia and/or acute bronchitis, smoking cigarettes or being a substance abuser, any illness in which the medications could not be stopped, occurrence of any severe side effects of N-acetylcysteine (stomatitis, nausea and rhinorrhoea), use of any kind of antioxidant drugs, and deterioration of clinical conditions during the course of the study.

All patients received 1200 mg of N-acetylcysteine or placebo daily in two divided doses for 4 months. Patients were not allowed to use any other treatments for at least 1 month before and during the course of the trial, but inhalatory salmeterol (50 μg, twice a day) and fluticason(250 μg, twice a day) was taken by all the patients.

In this study, we only enrolled participants in class 0 of bronchiolitis obliterans syndrome [16].

The study was done under double-blind conditions (i.e. neither the investigator nor the patient knew to which group they were assigned). N-Acetylcysteine tablets and placebo tablets looked identical, and were packaged and labelled, so they could not be identified. The steering committee and data management unit were masked to the treatment allocations during the study.

The patients were compliant if they took at least 80% of tablets. Drugs were delivered to them every 14 days, and they were instructed to bring their tablets with them to every visit, so that compliance was assessed at every visit by counting the returned boxes. The compliance check did not take place in the presence of the patient, and the number of returned tablets was recorded in the case-report form.

All patients were visited by a general practitioner before and after the trial in order to assess the clinical condition of each patient and presence and severity of dyspnoea, wake-up dyspnoea, cough and sputum. These symptoms (except for sputum) were quantified by a scale of 1–5 in which 1 denoted 'no problem' and 4 or 5 denoted 'the worst condition'. The questionnaire is depicted in detail in table 1. Sputum was reported as 0 for absence and 1 for presence. By this method, we were able to analyse the changes in clinical conditions during the course of the trial in placebo and N-acetylcysteine groups and the differences between these two groups.

High-resolution computed tomography (HRCT) was obtained from the participants before administration of the medications. Chest HRCT scanning was performed by High Speed Advantage Scanner (General Electric Medical System, Milwaukee, WI, USA). It consisted of five 1.0-mm collimation images obtained during deep inspiration and full expiration, while the patients were in supine position. All chest HRCT scans were reviewed by a radiologist familiar with bronchiolitis obliterans cases. The expiratory images were assessed for the presence of air trapping and its lobar distribution, defined as alteration of normal anterior–posterior lobar attenuation gradients and/or lack of homogenous increase in pulmonary attenuation, resulting in persistent areas of decreased attenuation. The presence of air trapping was quantified and was considered to be an indication of bronchiolitis obliterans only if it exceeded 25% of the cross sectional areas of an affected lung, in at least one scanned level [7].

All participants underwent spirometry (by a HI-801 Chest M.I. Spirometer, Tokyo, Japan) at a screening visit and afterwards at 2 and 4 months. The Spirometer was calibrated using the device provided by the manufacturer company. To assess the pulmonary function, we measured forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) and FEV1/FVC ratio. Firstly, we assessed these variables at the beginning of the trial. Afterwards, to reveal the effect of N-acetylcysteine, we subtracted FEV1 measured at the second month from the initial FEV1 (2, 0); subtracted spirometry variables measured at the fourth month from the initial ones (4, 0); and subtracted spirometry variables measured at the fourth month from the variables measured at the second month (4, 2) and compared these variables between the two groups.

Statistical analysis. In order to find out whether or not N-acetylcysteine was more effective than placebo on cough, dyspnoea and wake-up dyspnoea after 4 months, we compared 'delta value' (i.e. symptom score after 4 months – symptom score before the trial) between the two groups. Negative values indicated improvement in each symptom. For sputum, as mentioned above, negative values indicated improvement, positive values indicated worsening and zero indicated no change in the condition. All analyses were done with SPSS for windows version 13.0 (SPSS Inc., Chicago, IL, USA). Clinical data and delta values were analysed by applying t-test and Mann–Whitney *U*-test. Sputum was analysed by applying chi-square test. The changes of Spirometry parameters in both groups were compared applying repeated measure ANOVA (General Linear Model). Alpha less than 0.05 was considered statistically significant.

Table 1.

Definition of scales which were used to quantify cough, dyspnoea and wake-up dyspnoea in the patients.

Cough
1 I did not have cough
2 I have cough, but it is not a serious problem
3 I have cough, sometimes disturbs my work
4 I have disturbing cough, usually disturbs my work
5 I have disturbing cough, always disturbs my work
Dyspnoea
1 There is no dyspnoea
2 Dyspnoea only in extraordinary exercises
3 Dyspnoea in ordinary exercise
4 Dyspnoea in mild exercise
5 Dyspnoea in rest
Wake-up dyspnoea
1 I never woke up due to dyspnoea
2 I wake up less than once a week
3 I wake up once a week
4 I wake up more than twice a week

Result

After 4 months of treatment, 14 patients in the placebo group and 20 in the N-acetylcysteine group refused to continue the

Table 2.

Clinical characteristics of both N-acetylcysteine (NAC) and placebo groups at the beginning of the trial before drug administration.

	NAC	Placebo	Analysis
Cough[1]	2.88 (0.54)	2.78 (0.53)	P = 0.294
Dyspnoea[1]	2.92 (0.62)	2.91 (0.50)	P = 0.932
Wake-up dyspnoea[1]	1.94 (0.72)	2.05 (0.68)	P = 0.420
Sputum[2]	76.9% (n = 40)	94.8% (n = 55)	P = 0.01

The difference between the two groups for each clinical condition was analysed separately. The test applied and the significance level are depicted in the rightmost column.

[1]Data are depicted as mean (S.D.).

[2]Data are depicted as percent (number) of patients with sputum.

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Table 3.

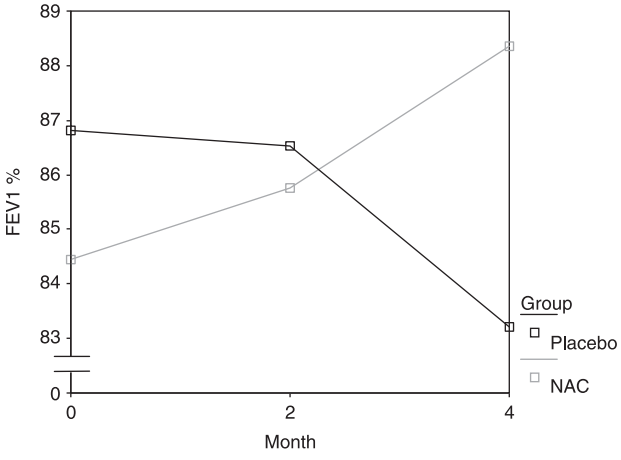
The effect of N-acetylcysteine (NAC) and placebo on clinical symptoms.

Symptom	Group	Before the study	After the study	Delta value	P-value
Cough	NAC	2.88 (0.54)	2.02 (0.31)	–0.86 (0.63)	<0.001
	Placebo	2.78 (0.53)	2.60 (0.65)	0.17 (0.88)	0.142
Dyspnoea	NAC	2.92 (0.62)	2.14 (0.34)	–0.78 (0.61)	<0.001
	Placebo	2.91 (0.50)	2.99 (0.68)	0.08 (0.72)	1
Wake-up dyspnoea	NAC	1.94 (0.72)	1.37 (0.48)	–0.57 (0.64)	<0.001
	Placebo	2.05 (0.68)	2.13 (0.50)	0.07 (0.84)	0.532

follow-up. None of these patients met our exclusion criteria. Patients who left the study were excluded from all analysis. Age did not differ significantly between the two groups (mean ± S.D. = 44.94 ± 11.39 years in N-acetylcysteine, 46.68 ± 11.29 years in placebo, P = 0.422). The height and weight of these two groups did not differ significantly (P = 0.69 and 0.20, respectively). The number of men and women in both groups did not differ either [37 (71.1%) men in the placebo group; 32 (61.5%) men in the N-acetylcysteine group, P = 0.85].

Clinical data.

Clinical characteristics of both the N-acetylcysteine and the placebo groups at the beginning of the trial are shown in table 2. The effects of N-acetylcysteine and placebo on the cough, dyspnoea and wake-up dyspnoea is shown in table 3. Sputum production was slightly higher in the placebo group at the beginning of the trial, as 76.9% (n = 40) in the N-acetylcysteine group and 94.8% (n = 55) in the placebo group revealed this symptom (chi-square test, P = 0.01). After 4 months, N-acetylcysteine reduced sputum production from 76.9% (n = 40) of cases before the trial to 9.6% (n = 5) of cases after the trial (McNemar's test, P < 0.001). Placebo also reduced sputum production after the trial [94.8% (n = 55) before the trial, 63.7% (n = 37) after the trial, McNemar's test, P < 0.001].



	FEV1 (0)	FEV1 (2)	FEV1 (4)
NAC	84.44 (9.33)	85.76 (10.92)	88.35 (11.83)
Placebo	86.80 (9.72)	86.53 (11.54)	83.19 (13.30)

Fig. 1. The upper part represents the mean of FEV1 in the N-acetylcysteine (NAC) group (grey, continuous line) and the placebo group (black, continuous line) at the beginning (month 0), after 2 months of the beginning of the trial (month 2) and after 4 months of the beginning of the trial (month 4). The table in the lower part reports the mean (S.D.) of FEV1 in both groups over time.

Pulmonary function test data.

FEV1. Although FEV1 increased significantly over time in the N-acetylcysteine group (P < 0.0001), and decreased in the placebo group (P = 0.007), there was no significant difference between these changes during the trial (P = 0.728). Considering the differences of FEV1 in both groups at the beginning of the trial in the regression model, N-acetylcysteine significantly improved FEV1 compared to placebo after 4 months (P < 0.0001; fig. 1).

FVC. There were not any significant differences between the changes in both groups over the course of trial (P = 0.664). But FVC changed significantly with time in the N-acetylcysteine group (P = 0.010), but not in the placebo group (P = 0.283). Considering the differences of FVC in both groups at the beginning of the trial in the regression model, N-acetylcysteine significantly improved FVC over placebo after 4 months (P = 0.014; fig. 2).

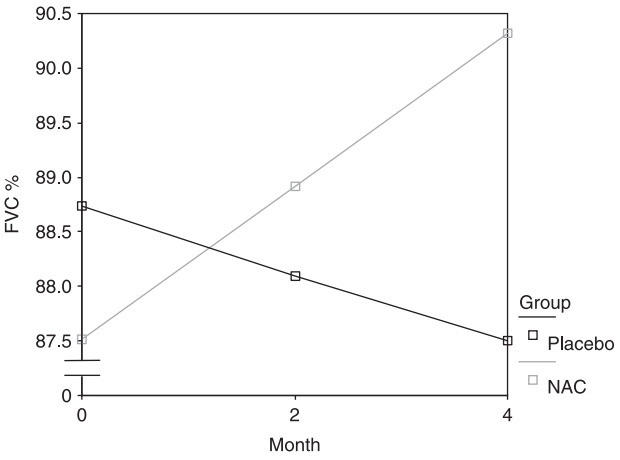


Fig. 2. The upper part represents the mean of FVC in the N-acetylcysteine (NAC) group (grey, continuous line) and the placebo group (black, continuous line) at the beginning (month 0), after 2 months of the beginning of the trial (month 2) and after 4 months of the beginning of the trial (month 4).

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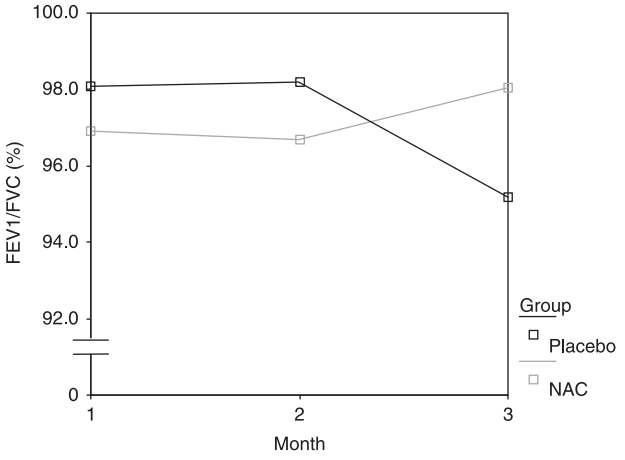

	FEV1/FVC (0)	FEV1/FVC (2)	FEV1/FVC (4)
NAC	96.92 (7.64)	96.70 (6.99)	98.03 (6.74)
Placebo	98.07 (7.57)	98.20 (8.17)	95.19 (10.16)

Fig. 3. The upper part represents the mean of FEV1/FVC in the N-acetylcysteine (NAC) group (grey, continuous line) and the placebo group (black, continuous line) at the beginning (month 0), after 2 months of the beginning of the trial (month 2) and after 4 months of the beginning of the trial (month 4). The table in the lower part reports the mean (S.D.) of FEV1/FVC in both groups over time.

FEV1/FVC. There were not any significant differences between these changes during the trial (P = 0.962). FEV1/FVC did not change significantly over time in the N-acetylcysteine group (P = 0.126), but decreased significantly in the placebo group (P = 0.006). Considering the differences of FEV1/FVC in both groups at the beginning of the trial in the regression model, N-acetylcysteine significantly improved FEV1/FVC over placebo after 4 months (P = 0.003; fig. 3).

Discussion

In this study, we found that N-acetylcysteine improved not only the clinical symptoms of the patients with sulfur mustard-induced bronchiolitis obliterans, but also the parameters of pulmonary function test. These findings are more interesting when we consider the time of the exposure to sulfur mustard and the time of the administration of N-acetylcysteine, that is, a gap of 18 years and treatment for only 4 months.

Previous studies have shown that N-acetylcysteine could be effective in the treatment of and control of clinical conditions in COPD patients by its antioxidative properties [17–19], and could also reduce bronchial infections [20] and exacerbations [21] in these patients. It seems that N-acetylcysteine interacts with inflammatory processes underlying the pathophysiology of COPD [22–24]. Because N-acetylcysteine resulted in a decrease in sputum production and dyspnoea in this study, we assume that its effect is inclusive.

N-Acetylcysteine is a potent antioxidant agent that acts as a pro-drug for cysteine and glutathione. This mechanism of action has been proposed as a possible basis for its use in bronchopulmonary disease [25]. N-Acetylcysteine may produce effects by preventing the release of many inflammatory mediators in different pathological conditions [9,10]. Several studies have shown that it can prevent bronchiolitis in mice exposed to cigarette smoke [26], reduce the level of tumour necrosis factor-α in lung-transplanted persons [27], protect bronchial epithelial cells against sulfur mustard *in vitro* [28,29], and also treat acute lung injuries induced by mustard gas in a rat model [30]. This is in line with the evidence that shows the effectiveness of antioxidants in preventing sulfur mustard-induced oxidative stress [31,32].

We enrolled patients in class 0 of bronchiolitis obliterans syndrome grade 0 in which FEV1 is equal to or more than 80% of baseline. Although their FEV1 is in the normal range, we also found that N-acetylcysteine could improve their FEV1. The current data cannot be used to make conclusions about the mechanism of a potential increase in FEV1, although its effect on reducing the secretion of many inflammatory modulators [33] and on prevention of respiratory airways thickening and bronchial smooth muscle hypertrophy [34] might be implicated.

We noticed a decrease in FEV1/FVC in the placebo group of this study. It might be due to the cassation of taking self-prescribed medications, which is commonly practiced among the patients to relieve the symptoms of their chronic disease.

Long-term studies on pulmonary function deterioration always have several drawbacks, which might hinder data interpretation. The main difficulty was drop-out with an overall of 21% in our study. All our drop-outs were due to the patients' refusal of follow-up. As none of the patients who left the study met our exclusion criteria, we assume that their fear for worsening their symptoms due to the stoppage of the routine medications altogether with increased anxiety and depression after exposure to both high-intensity warfare and chemical weapons might be the reason [35].

We administered N-acetylcysteine or placebo in combination with fluticasone and salmeterol. Because both groups received fluticasone and salmeterol, we cannot rule out the possibility of synergistic effects of N-acetylcysteine and these medications. We suggest that this possibility is not important as previous results in our clinic have shown that fluticasone and salmeterol had improving effects on only 27% of the studied patients with the same conditions as this study [36]. Hence, planning a clinical trial with N-acetylcysteine administration without any other types of medications would solve this ambiguity.

In conclusion, we noted that not only 1200 mg oral N-acetylcysteine per day can be used in treating bronchitis, but also in treating bronchiolitis. It also prevents sulfur mustard-induced oxidative stress besides treating sulfur mustard-induced pulmonary disease. Although N-acetylcysteine improved lung function in non-smoking bronchiolitis obliterans patients in our study, the effect of this drug on non-smoking COPD patients should be assessed in future trials.

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