Original Article

Efficacy of Adding Oral N acetyl Cysteine Supplement to the Cystic Fibrosis Treatment Regimen: A Randomized Quasi-Experimental Trial

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ABSTRACT

Objective: This study investigated the efficacy of adding the oral N-acetyl cysteine (NAC) supplement to the cystic fibrosis (CF) treatment regimen compared to adding a placebo. It also studied the quality of life and respiratory indicators of patients aged 6–18 with mild-to-moderate pulmonary involvement. **Methods:** This clinical trial was a randomized, quasi-experimental pilot and add-on therapy controlled with a placebo for 3 months. The case group received 200 mg of oral NAC three times a day. In contrast, the control group had a placebo in the same way. From the 2021 fall to the summer of 2022, 38 CF patients referred to Imam Hossein Children's Hospital Clinic were finally examined. They were clinically stable with a forced expiratory volume in the first second (FEV_1) level of more than 50% and no history of underlying cardiovascular and renal diseases. **Findings:** The differences between the groups were not significant. In the placebo group, key measures remained unchanged, whereas the NAC group had an improvement in the CF Questionnaire-Revised score but no notable changes in other indices. Overall, comparisons of forced vital capacity (FVC) between the groups showed no variation. **Conclusion:** The indicators of FEV_1, FVC, FEV_1/FVC, *forced expiratory flow between 25% and 75% of vital capacity*, and the quality of life of the case group were not significantly different from those of the placebo group, and no significant differences were observed between this medicine and placebo.

KEYWORDS: *Cystic fibrosis, N-acetyl cysteine, quality of life*

INTRODUCTION

Cystic fibrosis (CF) is known as a worldwide problem that can cause death in young patients. This is an autosomal recessive disease, recognized as the most common hereditary disease that shortens the life span in Caucasians.[1,2]

In these patients, the CF transmembrane conductance regulator (CFTR) gene is present in all body tissues, which usually affects several organs, most notably the lungs.[3] Due to the obstruction that happens in the airways and as a result of the occurrence of infection and inflammation, structural damage of the airways is inevitable, and eventually, respiratory failure occurs; therefore, despite the available treatments, respiratory infections are one of the leading causes of death in CF patients.[4]

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In developed countries, the first stage of CF diagnosis is performed through newborn screening programs. For this reason, patients with CF are identified before they develop clinical symptoms. Sweat tests are considered the gold standard approach for CF diagnosis. Two positive sweat tests or identifying two CFTR mutations are the basis for a specific diagnosis in suspected patients.[5]

To prevent the pulmonary progression of the disease, respiratory therapy is initiated immediately after diagnosis. These aggressive treatments aim to

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control symptoms and prevent complications. Key strategies include inhalation medications, airway clearance methods, antibiotic therapy, bronchodilators, pancreatic enzyme replacement, anti-inflammatory medicines, CFTR modulators, nutritional therapy, and supplements.[5]

Supplements and nutrients such as Vitamin E, Vitamin C, beta-carotene, selenium, and N-acetyl cysteine (NAC), a source of glutathione, are recommended for CF patients. These can help maintain the oxidant-antioxidant balance in these patients. However, the positive effect of NAC on lung function[6] is not wholly specific.

Few studies have been conducted on this illness in Iran. Although the exact epidemiology of CF in this country is unknown, the number of registered patients in Isfahan in 2022 was about 113. The highest number of CF patients is found in the 1–5-year-old age group, whereas the lowest is in the over 20-year-old age group.[7]

This study investigated the efficacy of adding the oral NAC supplement to the CF treatment regimen compared to adding a placebo. The quality of life and respiratory indicators of patients aged 6–18 with mild-to-moderate pulmonary involvement were studied. Other goals of this clinical trial were statistical analysis of the forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), FEV_1/FVC, *forced expiratory flow between 25% and 75% of vital capacity* (FEF_{25-75}) indices, and the respiratory index of quality-of-life CF Questionnaire-Revised (CFQ-R) in the case and control groups before and after the study.[8-10] In simpler terms, we aimed to compare the placebo group with NAC, placebo, and NAC outcomes separately before and after the examination. Possible side effects in the case group during and after treatment were also documented.

Methods

This study was a randomized, quasi-experimental, pilot, and add-on therapy clinical trial controlled with a placebo in 3 months. Thirty-eight CF patients referred to the University Children's Hospital affiliated with Isfahan University of Medical Sciences were finally evaluated. This project was found to be per the ethical principles and national norms and standards for conducting Medical Research in Iran, and its approval ID is IR.MUI.MED.REC.1400.218 (approval date: 2021-06-20). The Iranian Registry of Clinical Trials (IRCT) code for this clinical trial is IRCT20090808002306N7.

According to a similar study, because this disease is very rare in the community, this study was designed as a pilot and had a limited sample size of 18 people in the case group and 20 in the control group.[9]

The time of sample collection was from fall 2021 to summer 2022. The study location was the CF Clinic of Imam Hossein Hospital. The inclusion criteria for participants were as follows: a sweat test chlorine level of 60 mEq/L or higher, a genotype with two CF diagnostic mutations, at least one stable clinical symptom of CF, ages 6–18 years, FEV1 level above 50%, mild-to-moderate illness with stable clinical condition, no acute respiratory infections, no pulmonary symptom exacerbations within 14 days before the examination, ability to perform spirometry based on American Thoracic Society criteria, no concurrent medications affecting the disease outside the official treatment protocol, and no history of underlying cardiovascular or renal diseases.

Exclusion criteria were unwillingness to continue treatment and withdrawal from participating in the research plan, sensitivity to NAC or its pharmaceutical formulation, noncompliance with medication orders for at least 1 week, daily use of corticosteroids or nonsteroidal anti-inflammatory medicines within 4 weeks of the study or 72 h before the patient's visit, and the inability to swallow pills in a patient who had this ability before the research.

The convenient method was used to collect data. During treatment and follow-up, the participants were sampled using the census method. Randomization was done using the patient's date of birth, and all eligible admitted people were divided into two groups of 20 and 18 people: Control and case. Then, according to the order of the numbers, depending on whether the number was even or odd, a treatment regimen with or without NAC was assigned for each person.

Patients were randomly divided into two groups (case and control). Both groups had the standard treatment, and the case group also received oral NAC (200 mg tablet every 8 h) for 3 months. In contrast, the control group had a placebo in the same way. The pill-counting method was used during patient follow-ups to ensure the correct use of the medicine. If patients had more than a 40% difference from the expected remaining number of pills, they were excluded from the study.

Before entering patients into the study, the clinical trial procedure was fully explained to the children and their parents, and the consent form was provided to both the child and adolescent patients and their parents or legal guardians.

Two hundred milligram NAC tablets with the trade name of Mucosolvin® were used for the case group, and a placebo (including lactose, dicalcium phosphate, magnesium stearate, PVP K30, erosil, avicel, and starch) was provided to the control group.

Before starting and after completing the study, patients in both groups completed the spirometry test, and the indicators mentioned in the intended goals were recorded. The quality-of-life level of these patients was also measured using the CFQ-R questionnaire. This trial used Spirolab ®, a portable spirometer with an oximetry option.[11]

The CFQ-R was used to evaluate the quality of life of CF patients. The measurement method is based on a numerical scale from 0 to 100; the closer the number is to 100, the higher the quality of life. The CFQ-R is based on different indices. This study reviewed and scored the respiratory criteria using the CFQ-R questionnaire software.[12]

For statistical analysis, we used SPSS version 26 software. After inputting the data, we determined descriptive statistics (e.g., mean ± standard deviation, median, range). In this clinical trial, we used the Kolmogorov–Smirnov test, independent t, Wilcoxon, Mann–Whitney *U*, and paired sample *t*-tests to analyze final data. We aimed to compare the placebo group with NAC, placebo, and NAC outcomes separately before and after the examination. The confidence interval was set at 95% for variable comparisons, and for two-sided tests, the *P* value had to be <0.05.

Results

This study recruited 113 CF patients referred to Imam Hossein Hospital in Isfahan City. Fifty-two patients were evaluated using a convenient method based on the specified entry and exit criteria. According to their dates of birth, 25 patients received NAC, whereas 27 took a placebo. Finally, 38 patients completed the study (18 received NAC and 20 received a placebo) [Figure 1].

Seven patients who were given NAC showed the complication of productive cough. Eight people who were given NAC showed dry cough, and one patient showed both. One person had a severe headache after taking the. One CF patient complained about the bitter taste of NAC and vomiting after swallowing. According to Table 1, the studied groups did not have a significant difference.

Table 2 shows the differences between the studied groups were insignificant. The mean FEF_{25-75} in the placebo group and the median of FEV_1/FVC and CFQ-R scores did not change remarkably. In the NAC group, the median of the CFQ-R score improved, but the median of FEV_1/FVC and the mean of FEV_1 and FEF_{25-75} did not show a notable change. Comparing the mean of FVC in the placebo group and the median of this index in the NAC group did not illustrate a variation.

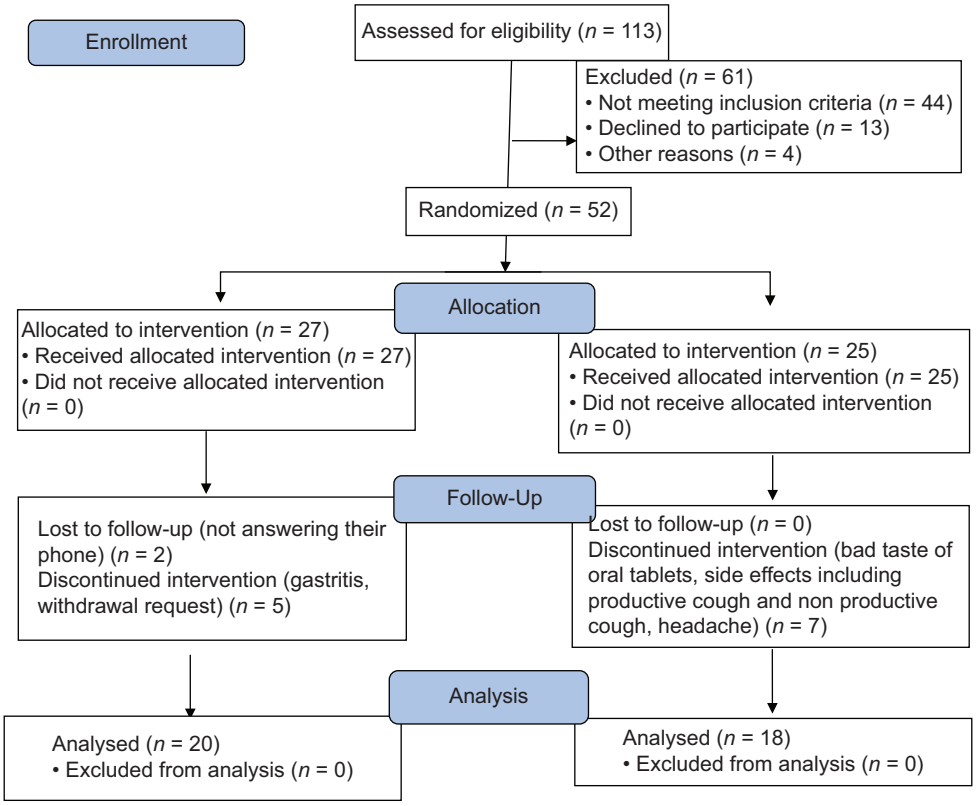

Figure 1: CONSORT flow diagram

Table 1: Characteristics of the studied cystic fibrosis patients

Variable	Groups				*P*
	Placebo (*n*=20)		NAC (*n*=18)		
	Mean±SD	Median (range)	Mean±SD	Median (range)	
Age (years)	9.75±3.2	9 (6–16)	10.1±3.5	10 (6–18)	0.78^{+}
Weight (kg)	27.8±12.9	24.2 (16–58)	28.3±11.8	24 (16.8–59)	0.74^{+}
Height (cm)	129.8±17.2	125.5 (103–159)	133.4±21	129 (103–187)	0.57*
FEV_1	86.4±18.7	86.5 (58–121)	82.44±14.87	84.5 (53–100)	0.48*
$FEF_{25–75}$	102.75±23.06	105 (66–147)	99±27.61	98.5 (61–167)	0.65*
CFQ-R score	78.05±21.28	83.33 (27.78–100)	78.05±23.67	85.83 (27.78–100)	0.98*

*Analyzed by independent *t*-test, $^{+}$Analyzed by Mann–Whitney *U*-test. NAC=N-acetyl cysteine, SD=Standard deviation, FEV_1=Forced expiratory volume in the 1st s, $FEF_{25–75}$=Forced expiratory flow between 25% and 75% of vital capacity, CFQ-R=The Cystic Fibrosis Questionnaire-revised

Table 2: Results of the studied groups before and after N-acetyl cysteine and placebo consumption

Variable	Time	Groups				*P* (between groups) - *P*
		Placebo (*n*=20)		NAC (*n*=18)		
		Mean±SD	Median (range)	Mean±SD	Median (range)	
FVC$^{\circledcirc}$	Before	80.10±20.68	79.00 (51–121)	77.50±15.16	78.50 (45–106)	0.260$^{\bullet}$
	After	85.20±18.02	85.00 (59–114)	77.50±14.42	81.50 (46–99)	
	P		0.073*		0.571^{+}	
$FEV_1$$^{\circledcirc}$	Before	86.40±18.70	86.5 (58–121)	82.44±14.87	84.50 (53–100)	0.171$^{\diamond}$
	After	90.70±17.25	90.50 (66–123)	82.94±16.94	88.50 (54–110)	
	P		0.104*		0.807*	
FEV_1/FVC$^{\circledcirc}$	Before	105.60±3.93	107.00 (98–113)	104.22±6.60	106.50 (91–113)	0.714$^{\bullet}$
	After	104.90±5.37	106.50 (88–113)	103.72±6.86	105.00 (89–113)	
	P		0.979^{+}		0.726^{+}	
$FEF_{25–75}$$^{\circledcirc}$	Before	102.75±23.06	105.00 (66–147)	99.00±27.61	98.50 (61–167)	0.740$^{\diamond}$
	After	103.80±28.00	101.50 (62–157)	100.50±32.76	109.50 (44–162)	
	P		0.791*		0.735*	
CFQ-R score$^{\circ}$	Before	78.05±21.28	83.33 (27.78–100)	78.05±23.67	85.83 (27.78–100)	0.305$^{\bullet}$
	After	76.38±23.69	83.33 (27.78–100)	84.56±17.72	88.89 (44.44–100)	
	P	0.717^{+}		0.260^{+}		

*Analyzed by the paired sample *t*-test, $^{+}$Analyzed by the Wilcoxon test, $^{\circledcirc}$Factors based on percentage predicted, $^{\circ}$Factors based on percentage, $^{\diamond}$Analyzed by the independent *t*-test, $^{\bullet}$Analyzed by the Mann–Whitney *U*-test. NAC=N-acetyl cysteine, SD=Standard deviation, FVC=Forced vital capacity, FEV_1=Forced expiratory volume in the 1st s, $FEF_{25–75}$=Forced expiratory flow between 25% and 75% of vital capacity, CFQ-R=The Cystic Fibrosis Questionnaire-revised

Discussion

This clinical trial investigated the effect of oral NAC (200 mg TDS) compared with placebo in 6–18-year-old Patients. After 3 months of taking their medicine, 38 people (18 had NAC and 20 had placebo) completed the experiment, and spirometry parameters and quality of life scores were evaluated.

According to Table 2, FVC had no meaningful variation in all groups. Although the number of patients examined in this study was less than in previous assessments, their results were confirmed. There has been no difference between the intake formulations. Dornase alpha appears to be more effective than NAC as a thiol derivative. Some of the studies had very small populations, so the possibility of error in the results increased.[13-20]

The difference of FEV_1 before and after the trial was insignificant in all groups. Previous studies had controversial results, but the effect of Dornase alfa was better than NAC. The reason for the difference with past experiments may include the variation in population (many of the mentioned studies had larger populations, and their results may be more accurate.). The difference in the inclusion criteria could affect the results (e.g., Ratjen *et al*. excluded the population of bronchodilator users). Other mucolytics need to be evaluated in more studies for better judgments.[11,13-28]

As in previous studies, FEV_1/FVC results showed no significant difference in all groups. Although trials in this field were minimal, the small sample size in these experiments could cause errors.[29] FEF_{25-75} showed no considerable difference in all categories. According to past trials, mucolytics did not significantly affect this index.[15,16,21,24,25,28] The CFQ-R score had no meaningful variation within groups before and after the study.

As most previous evaluations said, mucolytics did not significantly impact quality of life.[15,25,28]

According to Table 2, although the results were insignificant, the quality-of-life score rose with NAC intake, while the placebo did not.

In this trial, patients were from different places with dissimilar living and physical activity environments. Exercising can affect the progression of the illness, and we had children with different ranges of exercising, which can influence the results. CF in most patients gets worse with the aging process, so 18-year-old versus 6-year-old children have different signs (e.g., existing cough and the type of it, spirometry factors, physical activity, etc.) that can alter the results.

Limitations of this trial included the coronavirus pandemic and episodes of flu, a small number of CF patients (therefore, a small statistical population), and the long distance between the CF Center of Imam Hossein Hospital and the living places of some patients.

According to the results presented in this study, FEV_1, FVC, FEV_1/FVC, FEF_{25-75}, and the quality of life of the case group were not significantly different in the same groups, and no significant differences were observed between this medicine and placebo.

Studying NAC compared with a placebo in a different age range group (e.g., 7–15), using another formulation for this study that has easier swallowing (like effervescent tablets), Investigating the effect of pollution on CF patients and living in a populated city compared with a village are suggestions that may alter results of NAC administration in CF patients.

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Authors' Contribution

A. Sabzghabaee and M. Reisi designed the study. M. Reisi and M. Keivanfar prescribed tablets and evaluated the patients' clinical response to the treatment. S. Keshavarz collected the patients' data, monitored them during the intervention, and drafted the manuscript. A. Sabzghabaee and S. Keshavarz analyzed data.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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