N-Acetyl Cysteine in treatment of COPD

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Abstract

Introduction: In COPD excess expectoration secondary to tracheobronchial secretions contributes to symptoms, airflow obstruction and is diagnostic criterion. It also causes increased mortality, risk of hospitalizations and accelerated decline in FEV1. N-acetylcysteine (NAC) helps in liquefying mucus and DNA (via disruption of disulfide bonds) and has antioxidant effects.

Aims: Evaluate add-on effect of NAC on clinical-physiological parameters in COPD patients treated according to GOLD guidelines.

Material and Methods: Single labeled, randomized, parallel group prospective Observational study. In 120 stable COPD patients Modified medical research council (MMRC) dyspnoea score, COPD Assessment test (CAT score), number of exacerbations and hospitalizations in the last year were recorded and were randomized into 2 groups of 60 each. Group A received NAC 600mg twice daily along with standard treatment. Group B received standard treatment only. Mean and Standard Deviation was compared between groups using unpaired t-test. After 1 year, changes in above parameters were reassessed.

Statistical Analysis: Unpaired t-test and chi square test were used. Statistical significance was set at <0.05 level.

Results: MMRC score reduced from 3.37 study group) to 2.91, difference being -0.46, and in control from 3.37 to 1.18, difference of -0.22 and p value of p<.05. CAT score reduced more in test group (-4.4) than control group (-3.1), p=.02. Out of 40 exacerbations, 14 (35%) occurred in test and 26 (65%) in control group, reduction of 30% and p=0.01. Out of 28 hospitalizations 10 (36%) test group 18 (64%) control group. i.e. a reduction of 28% and p=0.06.

Conclusions: Use of N-Acetyl Cysteine, 600mg twice daily along with standard treatment can bring clinically significant change in CAT Score and frequency of exacerbations but not in MMRC score and hospitalizations.

Keywords: COPD exacerbation; Hospitalizations; N-Acetyl Cysteine; CAT; MMRC.

Introduction:

Chronic inflammation in airway and exposure to noxious particles or gases may lead to persistent respiratory symptoms and airflow limitation due to airways or alveolar abnormalities. The chronic inflammation due to high oxidative stress results in structural changes, narrowing of small airways and finally damage of lung parenchyma. Chronic obstructive lung disease (COPD) is a preventable and treatable disease as per the recommendations of global initiative for obstructive lung disease (GOLD) [1]. It is the third deadliest disease in US, killing more than 1,20,000 individuals yearly accounting more than 5% of the population. The treatment of COPD involves high cost resulting from frequent clinician visits, hospitalization and chronic therapy. There is an alarming increase in burden of the disease owing to air pollution, smoking among men and women. The different socioeconomic profiles, cultural practices and ethnicities lead to variability in COPD prevalence in the country as noted recently in the Indian Study on Epidemiology of Asthma, Respiratory Symptoms and Chronic Bronchitis in Adults (INSEARECH) involving total of 85105 men, 84470 women from 12 urban and 11 rural sites showing the prevalence in >35yrs to be 3.49%. Assessment of COPD requires determining severity of disease, its impact and risk of future events (exacerbations, admissions or death) on health and is essential to guide therapy [1].

Thick, tenacious secretion is always a major problem in COPD, although there is little evidence that thinning or increasing clearance induces clinical improvement. Some evidence supports modest benefit from oral thiol derivatives, other mucoactive agents, such as oral expectorants. There are no data to support mucolytic agents in COPD refractory to triple inhaler therapy.

Thiol derivative NAC an antioxidant and mucolytic agent designed to severe disulfide bonds of mucoproteins and DNA reduces mucus viscosity. PANTHEON trial with moderate to severe COPD (mean FEV1 49 percent of predicted) found reduction in exacerbations with NAC (600 mg tablets twice daily) compared with placebo. Based on the pantheon study, an oral thiol preparation NAC, 600 mg twice daily can be initiated on a trial basis and continued if there is symptomatic improvement especially in patients with significant sputum production, refractory to smoking cessation, routine therapies for COPD, and a course of antibiotics (when indicated). This study determines the effect of NAC over standard treatment in moderate to severe COPD patients in Indian patients.

N-Acetyl Cysteine (NAC), a thiol-containing compound, acts as mucolytic, antioxidant and has some anti-inflammatory properties [2]. Following oral administration, NAC is rapidly absorbed and metabolized to cystiene, a direct precursor in the synthesis of intra-cellular GSH [3]. Oral NAC

600mg/day for 5 days has shown to significantly increase GSH in bronchoalveolar lavage fluid when compared with those who did not receive NAC ($p<0.05$) 1–3 hours after the last dose [4]. NAC has shown direct and indirect impact in COPD on oxidative stress, frequency of cough, on dyspnoea, in number of exacerbations, effect on air trapping. Mucolytic properties of NAC are attributed to free sulphydryl (-SH) groups it contains, which splits disulphide linkages of mucoproteins in viscous mucus reducing viscosity and making it less tenacious [5]

Excess secretions combined with loss of mucociliary clearance, leads to mucus pooling that stimulates bacterial colonization, although precise role of bacteria in exacerbations is debatable. NAC directly prevents bacterial adherence to epithelial cells and is associated with low mucus bacterial count [6].

Material and Methods:

Study plan: Patients visiting the outpatient and inpatient department of Respiratory medicine in a Tertiary care hospital, which is affiliated to Deccan College of Medical Sciences, was included in the study. The efficacy of the NAC over standard treatment in treating COPD was assessed for 1 year i.e. from July 2015 to June 2016.

Inclusion criteria: Patients of 50-70 years of age diagnosed as stable COPD for at least 4 weeks before enrolment of study on basis of FEV 1 according to GOLD guidelines.

Exclusion criteria: Diagnosis of severe ischemic heart disease, chronic kidney disease, left heart failure, acid peptic disease, COPD stage IV, History of recent myocardial Infarction, stroke, severe hypertension, allergic rhinitis, bronchial asthma, any other concomitant respiratory illness apart from COPD, Patient on long term home oxygen therapy (LTOT) and those on long term corticosteroid therapy.

Eligible patients with COPD confirmed by routine diagnosis and Spirometry according to the GOLD guidelines were recruited in the study. After taking informed consent and complete physical examination, following basic routine investigations including chest X-ray, ECG, complete haemogram, liver function test, renal function test were performed. The data was collected in a predesigned Performa/questionnaire, which included age, sex, occupation, chief complaints, smoking status, BMI, mmrc dyspnoea score, CAT score, history of number of exacerbations in the last year & the number of hospitalizations in the last year.

Sample size:

The study protocol was reviewed by the Institutional Ethical Committee of Deccan College of Medical Sciences, Hyderabad and was granted ethical clearance. A total of 145 patients were selected. Out of which 25 patients were excluded based upon the exclusion criteria, as 8 patient had a history of allergic rhinitis and bronchial asthma, 5 patients were suffering from peptic ulcer, 3 patients had tuberculosis along with COPD, 2 patients had chronic kidney disease, 4 patients had very severe COPD (stage IV), and 3 patients did not give consent for the study.

Randomization:

Total of 120 patients who satisfied the inclusion criteria were randomly categorized into two groups.

Group A: (Test group)

This group comprised of 60 patients with moderate to severe stages of COPD. The patients were given NAC 600mg twice daily along with standard treatment.

Group B: (control group)

This group comprised of 60 patients who were prescribed the standard treatment only according to COPD severity and according to GOLD guidelines. Treatment was continued for a period of 1 year to observe any change with respect to clinical symptoms and physiological parameter.

Results and Analysis:

Both the control group and test group were followed for one year with three monthly periodic assessments.

Following findings were recorded every three months

1. Dyspnea -by Mmrc score
2. CAT score
3. Number of exacerbations if any occurred during this time period.
4. Number of hospitalizations if any occurred during this time period.

Unpaired t-test and chi square test was used to obtain statistical significance between the test and control groups, and $p<0.05$ -+was considered significant.

Results

The data showed the prevalence of COPD was seen mostly in elder patients. The enrolled patients were in the age range of 50-70 years. The mean age both in test and control groups was found to be 60 ± 4.79 and 60 ± 5.13. The frequency of affected COPD patients was 36% in age range of 61-65 years. Among the patients, there was male preponderance. The male to female ratio was found to be 3:2. Out of 120 patients, 82 (60%) were males and 38 (40%) were females (Fig. 1).

The common risk factor in COPD patients was found to be smoking. Out of 120 patients, 80 were smokers i.e. 52 were current smokers and 28 were ex-smokers. In the test group 25 (42%) and in control group 27 (45%) were current smokers. However, there were equal number of ex-smokers in both the groups i.e. 15 (25%). Among 120 patients 40 were non smokers i.e. 20 (35%) in test and 18 (30%) in control group (Table 1).

There was significant change in BMI in both the groups. The frequency of body mass index less than 21 was found in 18 (30%) in test group whereas 20 (33%) patients in control group. BMI more than 21 was found

in 42 (70%) in test and 40 (67%) in control group (Table 1).

The frequency of co-morbidities among the subjects was found to be 17 hypertension, 14 type 2 Diabetes mellitus, 10 CAD, 17 Osteoarthritis and 5 hypothyroid cases (Fig. 2).

The stage of GOLD was found to be 48% in moderate (GOLD II), 52% in severe stage (GOLD III) (Table 1). There was no significant change in both the cases.

The most common medication used in both the groups was Theophylline i.e. 45 (75%) in test and 48 (80%) in control groups. The other medications used in test and control groups were SABA 35 (58%) and 32 (53%), LABA 21 (35%) and 20 (33%) and the least used was ICS 16(27%) and 14 (23%) (Table 1)

There was a significant difference in MMRC score in test group recorded at baseline (3.37±0.66) and after 1 year (2.9±0.79) (Table 2) (Fig. 3). However, no significant change was found in control group at baseline and after 1 year.

There was a significant decrease in CAT score in both the groups as recorded at baseline and after 1 year i.e 28.8±3.75 and 24±4.19 in test group and 29±3.28 and 25±3.15 in control group respectively (Table 2) (Fig. 4)

The percentage of hospitalization in test group was significantly higher in control group (64%) when compared to the test group (36%) ($p<0.001$) (Table 3) (Fig. 5)

The COPD exacerbation was minimum in test group 14 (35%) compared to the control group 26 (65%) (Table 3) (Fig. 6)

FEV1 was found to increase slightly in both the study groups after 1 year treatment but the increase was found more in the test group (+0.55) than the control group (+0.53), but the increment among the groups after receiving treatment was found to be not significant as $p>0.05$ ($p=0.94$).

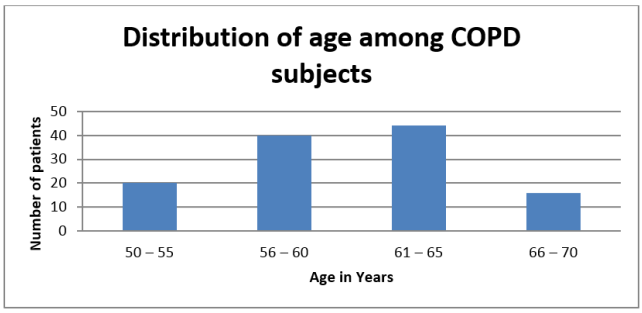

Fig. 1: Distribution of age among COPD patients

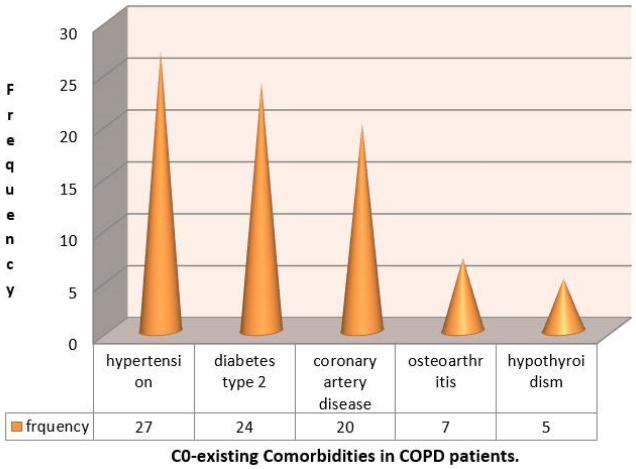

Fig. 2 : Co-morbities in COPD patients

Table 1: Variability of demographic data of COPD cases

S. No	Criterias	Test	Control
1	**Age in years**	60±4.79	60±5.13
2	**Gender**		
	Males	40 (67%)	42 (70%)
	Females	20 (33%)	18 (30%)
3	**BMI**		

	<21	18 (30%)	20 (33%)
	>21	42 (70%)	40 (67%)
4	**Smoking status**		
	Current smoker	25 (42%)	27 (45%)
	Exsmoker	15 (25%)	15 (25%)
	Nonsmoker	20 (33%)	18 (30%)
5	**Gold stage**		
	1	0	0
	2	30 (50%)	27 (45%)
	3	30 (50%)	33 (55%)
	4	0	0
6	**Medication**		
	SABA	35 (58%)	32 (53%)
	LABA	21 (35%)	20 (33%)
	LAMA	31 (52%)	30 (50%)
	ICS	16 (27%)	14 (23%)
	Theophylline	45 (35%)	48 (80%)

Table 2: Mean and Standard deviation of clinical and physiological parameters of study groups recorded at baseline and after 1 year

Score	Test		Control	
	Pre (Baseline)	**Post** (1 year)	**Pre** (Baseline)	**Post** (1 year)
MMRC	3.37±0.66	2.9±0.79*	3.37±0.69	3.18±0.77
CAT	28.8±3.75	24±4.19*	29±3.28	25±3.15*

*p<0.05

Table 3: Hospitalization and COPD exacerbation in both the groups

Parameter	Test	Control
Hospitalization	10 (36%)	18 (64%)
COPD exacerbation	14 (35%)	26 (65%)

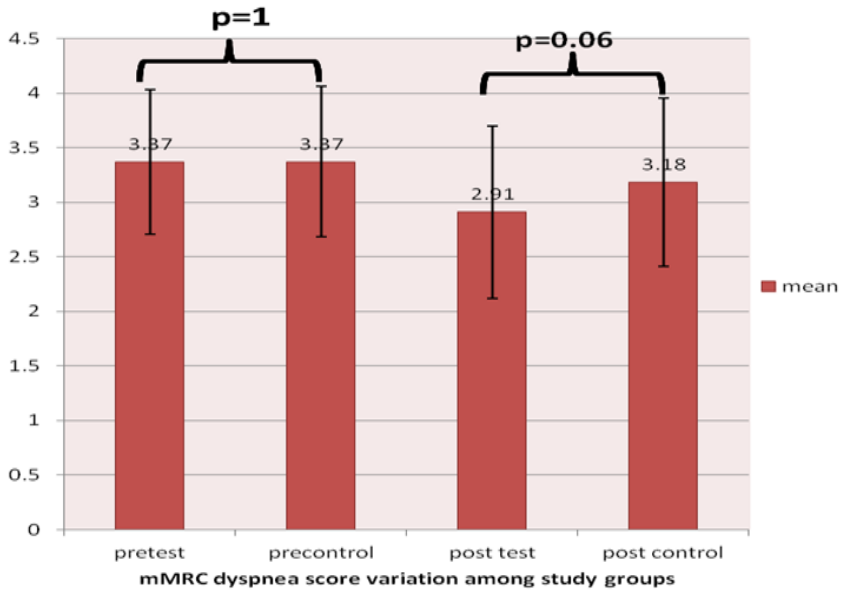

Fig. 3 Mean and standard deviation of mmrc score at baseline and after 1 year

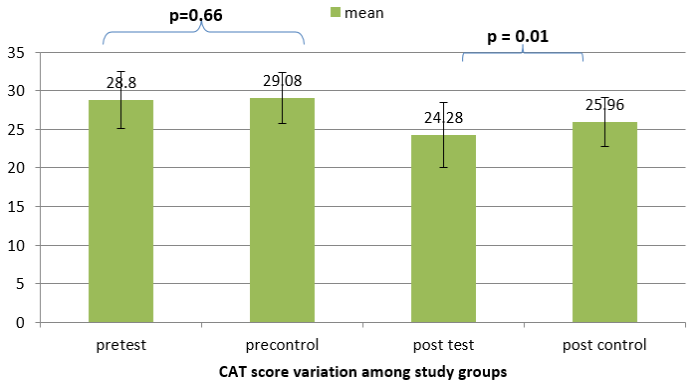

Fig. 4: Mean and standard deviation of CAT score at baseline and after 1 year

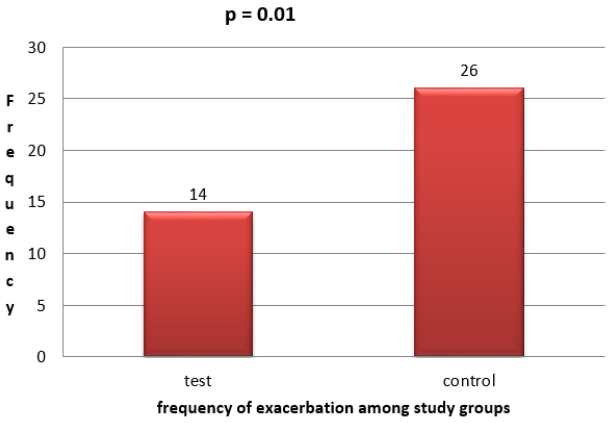

Fig. 5: Mean and standard deviation of frequency of exacerbation at baseline and after 1 year

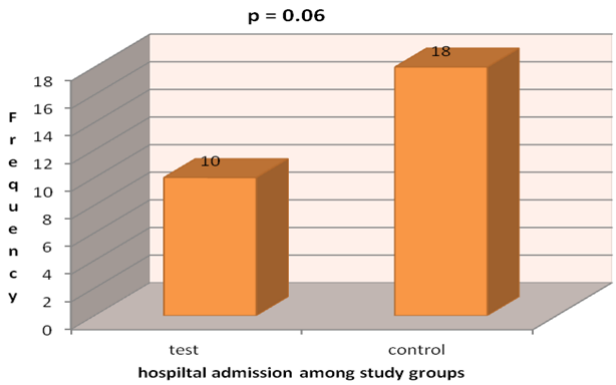

Fig. 6: Mean and standard deviation of hospitalizations at baseline and after 1 year

Discussion:

The (MMRC) scale, baseline dyspnoea index (BDI) are widely used tools for evaluation of limitation of activities due to dyspnoea in patients with COPD.

The present study was done to know the add on effect of NAC 600 mg twice a day on objective perception of dyspnoea score, number of exacerbations, number of hospitalizations due to exacerbations in moderate to severe COPD patients who are already receiving standard treatment based upon GOLD guidelines. These patients were then compared with similar moderate to severe COPD patients who are only receiving standard treatment based upon GOLD guidelines.

Effect of NAC on dyspnoea:

Tse et al study showed no difference between NAC and placebo in terms of respiratory symptoms (mMRC dypsnea score) [7]. Aylward et al reported that NAC decreased dyspnoea in COPD in comparison with placebo during long term oral treatment which may be partly caused by the mucolytic effects of NAC leading to increase in sputum volume and pour ability [8].

In this study MMRC dyspnoea score was found to reduce from 3.37 to 2.91 in the NAC treated group, and the difference from baseline to after 1 year was -0.46, MMRC score in control group also reduced from 3.37 to 1.18 and the difference from baseline was -0.22, which was less than the NAC treated group, but the reduction in both the groups was not statistically significant as p>0.05 (p=0.051).

Table 12: Previous studies showing effect of NAC on dyspnoea

Study	Effect of NAC on dyspnoea
Tse et al	No improvement in Mmmrc dyspnoea score
Aylward et al	Decreases dyspnoea in chronic bronchitis
Present study	No improvement in Mmrc score

NAC failed to demonstrate the beneficial effect on dyspnoea. Unlike bronchodilators, NAC acts in COPD through its antioxidant, anti-inflammatory and mucolytic properties. Therefore, NAC might not relieve dyspnoea directly in patients with COPD. However, the improvement of respiratory function would be another possible beneficial effect of high-dose NAC that, while needing further confirmation in larger studies, opens new and interesting perspectives for the use of NAC in COPD.

Effect of NAC on quality of Life:

FEV1 hardly correlates with dyspnoea, which is closely related to the patient's quality of life, which can vary among the patients with the same degree of airway obstruction. Dyspnoea on the other hand may reflect more comprehensive information than airway obstruction in patients with COPD and should be taken into account while evaluating the successful treatment [9]. GOLD primarily recommends the use of the COPD Assessment Test (CAT), has a broader coverage of the impact of COPD on patient's daily life and well-being. Other symptoms scales can be used where available, for example, the Clinical COPD questionnaire, and future GOLD updates are likely to expand in this area.

In this study, effect of NAC on health related quality of life or COPD related symptoms such as cough, expectoration, chest tightness, ability to do regular activities was evaluated by means of COPD ASSESSMENT TEST questionnaire.

Pela et al, reported improvement in 65% of the treated patients in quality of life in NAC group compared with 29% in placebo group (p<0.01) [10].

Another Multicentre study[11], showed improvement in clinical symptoms as a result of treatment with NAC which was a long-term double-blind trial with parallel groups conducted in several centres to which 744 patients with chronic bronchitis were recruited. Patients were randomly divided into two groups, one treated with NAC and the other with placebo. The results confirmed the efficacy of NAC regarding the parameters related to bronchial hyper secretion [11,12].

Tattersall et al, in an open clinical trial including 1,392 patients demonstrated the efficacy of NAC at a dose of 600 mg/day in reducing the viscosity of expectorations, promoting expectoration and reducing the severity of cough. After 2 months of treatment with NAC, the viscosity of expectorations improved in 80% of cases, the nature of the expectorations improved in 59%, difficulty in expectorating improved in 74% and the severity of cough improved in 71% [13].

Stey et al [14], systematic review of RCTs also addressed the effect of NAC in chronic bronchitis, rather than COPD per se symptoms. For each trial, the percentage of patients reporting improvements in symptoms was higher in NAC treated individuals than in those in the placebo arm. The difference in favor of NAC reached statistical significance in another large clinical trial, consisting of 611 patients (66% of the total number of patients in all trials considered) [11]. The authors of the meta-analysis concluded that of 100 treated patients, 26 would report that the NAC treatment led to improvement of their bronchitis-related symptoms, who would not have done so had they all received placebo [15]. Earlier systematic review also suggested that mucolytics improved symptoms in patients with chronic bronchitis but a subsequent meta-analysis suggested that NAC had no significant effect on quality of life [16]. Likewise, in the large BRONCUS trial [17], NAC (600 mg daily) did not improve results on the St George's Respiratory Questionnaire (SGRQ) over a 3-year period. In contrast, the recent PANTHEON study [18] with its larger sample size (n=1,006) and a higher dose of NAC (1,200 mg daily) demonstrated that chronic use of high-dose NAC could significantly improve the isolated "symptom domain" on the SGRQ (−3.37, *P*=0.043) in Chinese patients with COPD over one year, albeit without reaching the minimum clinically important difference.

Tse et al [7] showed no differences between NAC and placebo in terms of quality of life (SGRQ), as p value was not significant.

In this Study, CAT score was found to reduce in NAC treated group from 28.8 to 24.18, and the difference from baseline was -4.4, and in the control group, CAT score reduced from 29.08 to 25.96, and the difference from baseline was -3.1, which is less than the NAC treated group. The reduction in CAT score in both the groups was found to be statistically significant as p<0.05.

Table 13: Studies showing effect of NAC on COPD symptoms or quality of life.

Study	Effect of NAC on health related quality of life or symptoms
Pela et al	improvement in quality of life

Multicentre study	improvement in symptoms
tattersal et al	Promotes expectoration and reduces cough
Broncus study	no improvement in SGRQ Score
Pantheon study	Improved isolated SGRQ but not overall
Tse et al	no improvement in quality of life
Present study	Improvement in CAT Score

Effect of NAC on frequency of exacerbations:

Tse et al showed that, chronic use of high dose NAC (1200mg daily for one year) reduced the COPD exacerbation rate (0.96 versus 1.71 exacerbations per year) in Chinese patients with COPD, when compared with placebo [7].

PANTHEON, a large multicentre, one year trial conducted in Chinese patients with moderate-severe COPD, clearly demonstrated that high dose NAC (1200mg daily) could reduce the frequency of exacerbations (1.16 versus 1.49, p=0.0011) and prolongs the time to second and third exacerbations in the NAC group when compared with the placebo group, with the beneficial effect being more prominent in those with moderate COPD than in those with severe COPD [18].

Pela et al results show that the number of exacerbations decreased by 41% in group of patients treated with NAC on top of standard treatment. In the group treated with standard therapy alone, 63 patients had at least one exacerbation in comparison with 46 patients in the group treated with NAC and standard therapy ($p < 0.003$) [10].

Similar study in India done by, Arshad et al showed that use of NAC, in patients >50 years reduces the frequency of exacerbation. The number of patients who had exacerbations in the study group was lower than those in the control group in the 1-year follow up period. Only 25 (50%) patients in the study group had at least 1 exacerbation as compared to 38 (76%) in the control group i.e. a reduction of 26% ($p<0.01$, statistically significant). 15 (30%)

of the patients in the study group had 2 or more exacerbations during the follow-up period as compared to 18 (36%) in the control group i.e. a reduction of 6% ($p>0.05$, statistically insignificant) [19].

Hansen et al also showed oral NAC 600 mg twice a day exerts a beneficial action in chronic bronchitis by reducing the number of exacerbations. The numbers of observed exacerbations were unexpectedly low in both groups. The number was lowest in NAC group, however, the difference did not reach statistical significance in the present study (p=0.08) [20].

In Grassi & Morandini et al, NAC 600mg daily, 3 days a week for 6 months, and a placebo have been compared in a double blind controlled trial, which showed significantly lower number of exacerbations. This study suggested that long term oral treatment with the mucolytic in chronic bronchitis may be useful as an alternative to long term antibiotic prophylaxis, or to complement brief courses of antibiotics, in addition to the usual physiotherapy [21].

In Rassmusen et al, of the 91 patients completing the trial 39 patients, 16 from the acetylcysteine group and 23 from the control group, had at least one exacerbation, and that the number of exacerbations as well as the number of exacerbation days was lowest in the NAC-treated group. This finding was noted both at the 4-month and 6-month of registration. Although the tendency was constant, neither of the differences reached the significance level [22].

However, the large 3-year BRONCUS study failed to demonstrate that NAC (600 mg daily) was beneficial in reducing the exacerbation frequency in patients with COPD, although it did suggest that NAC could reduce exacerbations in a subgroup of "inhaled steroid-naïve" patients with COPD and achieve a significant reduction in hyperinflation in patients with COPD on secondary analysis [17].

The systematic review by Poole et al concluded that oral mucolytics could reduce exacerbations in patients with COPD/chronic bronchitis by 0.48 episodes per patient-year, with a higher likelihood of these patients being exacerbation-free (odds ratio 1.84; 95% confidence interval 1.63–2.07) when compared with those treated with placebo. Similar results were obtained in our study where the exacerbation rate reduced by 30% in the NAC group [16].

This discrepancy may be attributable to the different doses of NAC used in the previous trials. In vitro and in vivo studies suggested that NAC could only exert its antioxidant effect at a low dose (less than 600 mg), while a larger dose (1,200 mg or above) was needed to exert its anti-inflammatory properties [23].

In this Study, Frequency of exacerbation was found to reduce more in the test group (30) than the control group (19) and statistically the change was found to be significant as $p<0.05$.

Table 14: Previous studies showing effect of NAC on frequency of exacerbation

Study	Effect of NAC on frequency of exacerbation
Tse et al	Decreased exacerbation rate
Pantheon	Decreased exacerbation rate
Pela et al	Decreased exacerbation rate
Arshad et al	Decreased exacerbation rate
Hansen et al	Decreased exacerbation rate
Grassi et al	Decreased exacerbation rate
Rasmussen et al	Decreased exacerbation rate but did not achieve statistical significance

Bronchus study	Did not decrease exacerbation rate except steroid naive patients
Poole et al	Decreased exacerbation rate
Present study	Decreased exacerbation rate and reached statistical significance

Exacerbation of COPD is multifactorial.NAC may contribute to a reduction in exacerbation frequency by acting at a number of target sites. It exerts its mucolytic function by reducing the viscosity of sputum and its secretion in the airways, which is important given that viscous sputum, together with consistently inflamed ciliated epithelial cells in the airways, are the preferred sites for bacterial attachment [24]. NAC could further inhibit the attachment of bacteria to the epithelium by disrupting the bacterial receptor sites on the epithelial surface and in mucus [25]. Patients with COPD have over expression of adhesion molecules (e.g., intercellular adhesion molecule-1, which causes excessive transmigration of neutrophils). It was shown in an in vitro study that NAC could exert its anti-inflammatory effect by inhibiting cytokines that stimulated IL-8 and intercellular adhesion molecule-1 in endothelial and epithelial cells1 [26].

Other effects of NAC that have been demonstrated include reduction of lysozyme and lactoferrin concentrations in smokers, reduction in the activation and number of neutrophils and macrophages in the bronchoalveolar lavage of smokers, and inhibition of adherence of bacteria to ciliated epithelial cells in vitro [27]. However, in recently published evidence-based guidelines on the prevention of acute exacerbations of COPD by American College of Chest Physicians and Canadian Thoracic Society, N-acetylcysteine therapy is also recommended (grade 2B) for patients with moderate to severe COPD and a history of two or more exacerbations in the previous 2 years. This evidence is also present in the GOLD recommendations.

Effect of NAC on hospitalisation:

Vestbo et al showed that chronic mucus hyper secretion is significantly associated with an increased risk of hospitalization of COPD patients [1]. Gerritis and colleagues concluded that NAC may decrease the risk of hospitalizations by about 30%. This reduction however needed minimal dose of 400mg/day in order to reach protective effect [5].

In an Indian study, Arshad et al which used NAC 600 mg daily, total number of hospital admissions was lower in study group 37 as compared to control group 55 and the reduction was found to be statistically significant ($p<0.05$) [19].

Pela et al showed total number of sick days was significantly less, 82 in the NAC group as compared with standard therapy group 155. This reduction, however, did not reach a statistically significant level due to the large variation [10].

In this study, rate of hospitalization was found to reduce more in the test group (17) when compared to the control group (10), but statistically change was not found to be significant as $p>0.05$.

Table 15: previous studies showing effect of NAC on hospitalization

Study	Effect of NAC on rate of hospitalizations
Geris et al	Decreases number of hospitalizations
Arshad et al	Decreases number of hospitalizations
Pela et al	Decreased number of sick days but it was not statistically significant
Present study	Decreased number of hospitalisations but did not achieve statistical significance

Strengths and limitations of study: Sample size in this study was small (120). Another limitation was that the patients were also receiving inhaled corticosteroid in combination with long acting β2 agonist, according to gold guidelines. TORCH study showed that inhaled corticosteroids along with β2 agonist decreased the frequency of exacerbations versus placebo, and improved quality of life, but didn't show any significant effect on survival in 3 years. So the findings of this study is very similar to TORCH study and as the patients in this study also received inhaled corticosteroid, so the beneficial effect of NAC in COPD patients cannot be clearly explained. Hence, further studies might be needed to evaluate the effect of NAC without the concomitant use of inhaled corticosteroid. In this study, effect of NAC was evaluated only in moderate-severe COPD patients. So the effect of NAC on mild and very severe COPD patients cannot be explained. Hence, further studies are needed to know the beneficial effects of NAC in mild and very severe COPD patients.

Recommendations for future study:

NAC can be used in higher doses as higher doses of NAC seem to be more effective in inflammation and oxidative stress modulation. Apart from this, use of derivatives of NAC is another available option [28].

A newly developed form of NAC, N-acetylcysteine amide(NACA), because of its neutral carboxyl group, NACA is lipophilic, cell permeating and has strong antioxidant and protective effects [28]. Nevertheless, more studies are necessary to assess the effectiveness of those derivatives in lung disorders in vivo. Because of the fact that higher doses of NAC seem to be more effective in inflammation and oxidative stress modulation with side effects, a change in administration pattern may be of importance. Furthermore, evaluating novel methods of drug delivery, inhaled NAC [28, 29], and use of NAC derivatives with better availability may result in more effective treatment. For example, N-

acystelyn (NAL) a lysine salt of NAC, has mucolytic and antioxidant properties. Its mucolytic activity is approximately equal to the sum of the activities of its two components, namely acetylcysteine and lysine and its antioxidant properties are comparable with those of NAC [30].

Conclusion and Summary:

Oral N-acetylcysteine 600mg b.i.d for 1 year

1. Reduces mmrc dyspnoea score but not a significant level.
2. Reduces frequency of exacerbations to a significant level.
3. Reduces hospitalization rate but not to a significant level.
4. Reduces CAT score in COPD to a significant level.

In addition to standard treatment in stable COPD patients NAC can be considered as a part of COPD management especially in cases with bothersome sputum production refractory to smoking cessation, steroid use and use of antibiotics if indicated.

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