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A Prospective Study on Effect of N-Acetylcysteine as Monotherapy vs N-Acetylcysteine and Acebrophylline as Combination Therapy in Chronic Obstructive Pulmonary Disease

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ABSTRACT

Chronic obstructive pulmonary disease is a heterogenous lung condition. It is mainly caused due to long-term exposure to harmful particles or gases, most commonly due to cigarette and smoking which is characterized by chronic respiratory symptoms (Dyspnea, cough and sputum production due to abnormalities of the airways. Among patients with chronic obstructive pulmonary disease, we aimed to compare the efficacy of N-acetylcystiene as monotherapy with N-acetylcysteine and Acebrophylline as combination therapy in the COPD patients aged of 25 and above. The main objective is to determine the N-acetylcysteine and Acebrophylline are safe and effective for individuals with chronic obstructive pulmonary disease and also to track the FEV1/FVC in patients using N-acetylcysteine and Acebrophylline.This is a prospective and observational study done after ethical committee approval. A total of 70 patients were included in the study. Out of 70 subjects which clearly indicates tha age group of >60 were highly affected by COPD. Shortness of breath, cough and fever were the most common symptoms. Females were more prone to COPD than Males. The most common risk factors were Hypertension, diabetes mellitus, bronchial asthma and hypothyroidism in which hypertension was (84.3), Diabetes mellitus (61.4), bronchial asthma (8.6) and hypothyroidism (12.9). The laboratory parameters such as pH day 1 (0.015), pH day -2(0.010) and pH day-3 (0.005) it shows statistically significant. PaCO2 on day-1(0.05), PaCO2 on day-2(0.03) and on day-3(0.01). HCO3 on day-1(0.030), HCO3 on day-2(0.020), HCO3 on day-3(0.010) and PaO2 on day-1(0.05), PaO2 on day-2 (0.03) and PaO2 day-3(0.01) all the laboratory parameters shows statistically significant difference. Our findings show that the progressive improvement of laboratory parameters with N-acetylcysteine and Acebrophylline as combination therapy in COPD. The analysis of this study showed a significant statistical P value of 0.01 which implies the effectiveness of N-acetylcysteine and Acebrophylline as combination therapy. This study demonstrates that N-acetylcysteine and Acebophylline as combination therapy shows highly effective and safe in Chronic obstructive pulmonary disease.

Keywords: Chronic obstructive pulmonary disease, N-acetylcysteine, Acebrophylline.

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INTRODUCTION

Chronic obstructive pulmonary disease is a heterogenous lung condition which is characterized by chronic respiratory symptoms (Dyspnea, cough and sputum production due to abnormalities of the airways (bronchitis, bronchiolitis). It is mainly caused due to long-term exposure to harmful particles or gases, most commonly due to cigarette and smoking [1, 2].

Chronic obstructive pulmonary disease is a combination of both conditions that is chronic bronchitis and emphysema. Chronic bronchitis is hypothesized to be caused by goblet cells' overproduction and hypersecretion of mucus. When exposed to harmful or infectious stimuli, airway epithelial cells release inflammatory mediators such interleukin 8, colony-stimulating factor, and other pro-inflammatory

cytokines. The release of regulating molecules such as angiotensin-converting enzyme and neutral endopeptidase decreases as well. In chronic bronchitis, the alveolar epithelium acts as both the target and the initiator of the inflammatory process. During an acute exacerbation of chronic bronchitis, the bronchial mucous membrane becomes hyperemic and edematous, and bronchial mucociliary function is reduced. This, in turn, impairs airflow due to luminal blockage in narrow airways. Debris clogs the airways, which exacerbates the irritation. In chronic bronchitis, the abundant flow of mucus causes the characteristic cough of the disease [8].

Emphysema causes damage to the lungs' air sacs and the walls that connect them. This causes the sacs to lose flexibility and instead trap air. It becomes progressively difficult to remove all air from the lungs, and they no longer function properly. This results in the presence of more air than normal. This condition, known as air trapping, causes the lungs to hyperinflation. When there is extra air in the lungs, breathing requires more effort, contributing to shortness of breath. Damage indicates that the air sacs that normally support the airways and breathing process are unable to properly expand during inhalation or exhalation. The injury may also destroy the walls of the air sacs, resulting in larger, less efficient air sacs instead of smaller ones. This decreases the exchange of gases within the lungs [9].

Severity of chronic obstructive pulmonary disease has been classified based on lung volumes done by spirometry. If the FEV1/FVC:<0.7 but FEV1% of predicted value:>80 it comes under mild. In moderate case the FEV1/FVC:<0.7 but FEV1% of predicted value:50-80. If FEV1/FVC:<0.7 but FEV1 % of predicted value:30-50 it can be considered as severe. In the very severe condition, the FEV1/FVC:<0.7 but FEV1% of predicted value:<30 [2]. Chronic obstructive pulmonary disease is a major cause of morbidity and mortality across the globe. According to World Health Organization estimates 65 million people have moderate to severe chronic obstructive pulmonary disease. More than 3 million people died of chronic obstructive pulmonary disease in 2005 corresponding to 5% of all deaths globally and it is estimated to be the third leading cause of death by 2030. Prevalence of chronic obstructive pulmonary disease-based on gender Out of the eight studies, gender-wise prevalence was reported in five studies. The prevalence of COPD among males and females were 11.4% (95% CI: 6.0%–16.9%) and 7.4% (95% CI: 5.2%–9.6%), respectively. We did not observe any decrease in heterogeneity among this sub-group. There was a significant difference in the heterogeneity [4].

Among the studies from India, the pooled prevalence of COPD was 11.1%. The authors determined that besides smoking, additional risk factors included exposures to biomass fuel, occupational dust and environmental tobacco smoke and a previous diagnosis of tuberculosis or asthma. By 2030, sustainable development goal is to reduce the premature mortality caused by non-communicable diseases through prevention and treatment [5]. Most of the information available on COPD prevalence, morbidity and mortality comes from high income countries. However, it is known that low- and middle-income countries already has much burden of COPD with almost 90% of COPD deaths taking place in these countries. In this issue, the joint ICS/NCCP consensus guidelines for the diagnosis and management of COPD have been published to facilitate the Indian practitioner in burden reduction, diagnosis and management of chronic obstructive pulmonary disease [6].

Chronic obstructive pulmonary disease occurs when the lungs and airways are damaged and irritated. It is frequently associated with long-term exposure to toxic chemicals like smoking, occupational exposures, air pollution, genetics-alpha-1 antitrypsin deficiency. Smoking is the leading cause of chronic obstructive pulmonary disease, accounting for approximately nine out of ten cases. The chemicals in smoking can injure the lungs and airways linings. Occupational exposures like cadmium dust and vapours, dust from gain and flour, potential hazards include silica dust and welding fumes, isocyanates and coal dust if exposure to any of those chemicals at workplace it can harm the lungs and raise the risk of developing chronic obstructive pulmonary disease. Long term exposure to air pollution can affect people who already have long illness. Apart from other factors it can also cause due to deficiency of Alpha-1 Antitrypsin. It is a pulmonary protectant. People with Alpha-1 antitrypsin deficiency often acquire COPD at an early age, especially if they smoke [12]. Signs and symptoms in COPD do not manifest until extensive lung damage has occurred and they usually worsen with time. COPD symptoms include: Shortness of breath, wheezing, tightness in the chest, chronic cough with sputum, lack of energy, repeated respiratory infections and unintended weight loss [11]. Chronic obstructive pulmonary disease diagnosed by various tests include: Chest X-ray, spirometry, complete blood picture, pulmonary function tests, ABG and sputum test [7]. Chronic obstructive pulmonary disease is treated with Bronchodilators, mucolytics, steroids and antibiotics.

The first and most important treatment of COPD in smokers is to stop smoking. Medications and other therapies are available.

Medications can also be prescribed to help relieve symptoms of COPD and to prevent symptom flares (called exacerbations) that can lead to further loss of lung function. Some general classes of medications include those that aim to widen the airways (bronchodilators), reduce swelling in the airways (anti-inflammatory drugs, such as steroids), and/or treat infections (antibiotics). Other than antibiotics, most COPD medications should be taken every day, usually for life. Stay as healthy as possible. Avoid contact with those who are sick, wash hands often, get a yearly flu vaccine, and get pneumonia and COVID-19 vaccines when recommended by the healthcare provider [14]. The potent medications that are prescribed in chronic obstructive pulmonary disease:

N-Acetylcysteine is a mucolytic agent, Acetylcysteine's sulfhydral groups may hydrolyze disulfide bonds within mucin, causing the oligomers to breakdown and the mucin to become less viscous. It also has antioxidant activity which helps to synthesize the antioxidant glutathione [15, 16]. The onset of action of N-acetyl cysteine is 5-10 minutes. The mean time to peak plasma serum levels is 1-2 hour. The volume of distribution is 0.47L/kg. N-acetyl cysteine of 66.97% protein bound in serum, usually to albumin and 13-38% of drug retrieved in the urine but just 3% is recovered in the feces. N-acetylcysteine can be administered orally and intravenously with doseage of 600-1200mg [17].

Acebrophylline as a bronchodilator it inhibits intracellular phosphodiesterase and promotes bronchial muscle relaxation by raising cAMP levels. The optimal concentration of acebrophylline obtained within 2 hours and half-life of the Acebrophylline is 4 to 9 hours. It can be metabolized in liver and excreted through urine. Acebrophylline would be administered orally with the dose of 100 mg [10].

In some people, COPD can also cause the oxygen level in the blood to be low. If this occurs, a person can be given supplemental oxygen. Breathlessness should not be confused with low oxygen levels. People with COPD can experience shortness of breath or have a hard time breathing even if they have good oxygen levels. Therefore, breathlessness is not always a good guide for whether you need to use oxygen.

Proper nutrition and staying in good physical shape are also important not just for symptom relief but also for quality of life. Pulmonary rehabilitation programs offer supervised exercise and education for those with breathing problems and should be a part of a comprehensive treatment plan for anyone with COPD.

MATERIAL AND METHIODS

Study protocol

This study was conducted at the Department of Pulmonology, Vidhyanagar after getting approval from the ethical committee. It was a prospective observational study with a sample size of 70 in the 6 months of duration conducted in tertiary care hospital, to study the efficacy and safety of N-Acetylcysteine as monotherapy vs N-Acetylcysteine and Acebrophylline as combination therapy in COPD patients.

Study design

Comparative and Prospective study design.

Study duration

This study was conducted from September,2023 to April,2024

Sample size

Complete enumeration of the available subject will be carried out for a span of 6 months. Sample size is of 70.

Study site

The study is conducted in pulmonology department at Dhurgabhai deshmukh hospital, vidhyanagar.

Study criteria

Inclusion criteria

- Patients age of more than 25 years and above
- Patient diagnosed with COPD

Exclusion criteria

- Patients below 25 years are been excluded.
- Patients other than chronic obstructive pulmonary disease are been excluded.
- Patients who are not willing to participate in the study.
- Patients who are pregnant and lactating mothers are excluded in the study.
- Patients with COPD-A (Emphysema) are excluded.

Data Collection

A review of all the relevant and necessary data will be collected from patient's records, laboratory records, Prescriptions and also by interviewing the patients. We have analyzed the data by using both inferential and descriptive statistics.

Statistical Analysis

The analysis of ABG levels, WBC count, eosinophills, NLR ration and FEV1: FVC was presented in Tables as numbers. Comparison between the laboratory parameters and treatment were done. Value of P <0.05 were considered significant [18,19].

RESULTS

The demographic data and patient characteristics in pulmonology department was enrolled in the study. The total number of 70 case reports were analysed and included during the study.

Distribution of subjects based upon age Table 1 shows

In a study of 70 subjects the mean of age over 60 was (54.3%), and 11.4% for those under 40. The age group of 40-50 had a mean of 34.3%. The maximum exposed age group are >60(54.3) within the total population. As increasing age, gradually changes occur in the lungs such as loss of lung elasticity, weakening of the chest wall muscles, decreased efficiency of the airways. These age-related changes make the lungs more susceptible to damage from irritants and contribute to development of COPD.

Table 1: Distribution of subjects based upon age

Age group	Frequency	Percentage
<40	8	11.4
40-60	24	34.3
>60	38	54.3
Total	70	100

Distribution of subjects based on gender Table- 2 shows

Among 70 subjects the mean of female group was 52.9% and the mean of male group were 47.1%. Based on the data females are more prone to COPD than males. It is because cigarette smoking it could be major factor, women generally have smaller lungs than men so at women can experience a more rapid decline in lungs function and other factors like exposure to indoor air pollution, hormonal influences, airway differences which means women tend to have smaller airways, which may make them more vulnerable to the effects of irritants.

Table 2: Distribution of subjects based on gender

Gender	Frequency	Percentage
Female	53	52.9
Male	37	47.1
Total	70	100

Distribution of subjects based on treatment Table-3 shows

Among 70 subjects the mean of monotherapy (47.1%) and for combination therapy (52.9%). It suggests that combination therapy shows high effective than monotherapy.

Table 3: Distribution of subjects based on treatment

Treatment	Frequency	Percentage
Monotherapy	33	47.1
Combined therapy	37	52.9
Total	70	100

Distribution of subjects based on complaints Table -4 shows

Among 70 subjects the subjects with shortness of breath (88.6%) are highly developed COPD than the subjects with cough (85.7%) and fever (65.7%).

Table 4: Distribution of subjects based on complaints

Complaints	Frequency	Percentage
Fever	46	65.7
SOB	62	88.6
Cough	60	85.7

Distribution of subjects based on past history Table-5 shows

Among 70 subject's hypertension (84.3%) is most common followed by diabetes mellitus (61.4%), bronchial asthma (8.6%), hypothyroidism (12.9%). Table 6 shows the distribution of subjects based on laboratory parameters by treatment

Table 5: Distribution of subjects based on past history

Past history	Frequency	Percentage
HTN	59	84.3
DM	43	61.4
Bronchial asthma	6	8.6
Hypothyroidism	9	12.9

Table 6 sows the distribution of subjects based on laboratory parameters by treatment

Table 6: Distribution of subjects based on laboratory parameters by treatment

Descriptive Statistics				
	Minimum	Maximum	Mean	Std. Deviation
pHday1	7.00	7.85	7.2500	.12000
pHday2	7.00	7.50	7.2800	.09000
pHday3	7.20	7.42	7.3200	.05000
PaCO2_day1	25.00	70.00	47.5000	7.50000
PaCO2_day2	34.00	54.00	45.5000	4.10000
PaCO2_day3	40.00	46.5	44.575	.9436
PaO2_day1	17.90	108.00	55.8449	11.27747
PaO2_day2	35.50	85.50	55.9893	6.29341
PaO2_day3	51.0	60.0	55.484	2.5130
HCO3_day1	14.20	57.70	22.9623	7.13152
HCO3_day2	18.00	20.00	18.8758	.54246
HCO3_day3	21.30	25.36	23.2220	.99977

Distribution of subjects based on pH in monotherapy and combined therapy Table-7 shows

Among 70 subjects the laboratory parameters are gradually improving pH on day-1 (0.015), pH on day-2 (0.010) and pH on day-3(0.005) which shows statistically significant difference. It proves that combination therapy is effective than monotherapy.

Table 7: Distribution of subjects based on pH in monotherapy and combined therapy

	Group	Mean	Std. Deviation	P value
pHday1	Monotherapy	7.2422	.10797	0.015
	Combined therapy	7.3500	.09000	
pHday2	Monotherapy	7.2475	.08682	0.010
	Combined therapy	7.3200	.06500	
pHday3	Monotherapy	7.3097	.04162	0.005
	Combined therapy	7.4000	.03000	

Distribution of subjects based on PaCO2 in monotherapy and combined therapy Table-8

It shows that PaCO2 on day-1 has (0.050), PaCO2 on day-2(0.045) and PaCO2 on day-3 0.035) which suggests that there is a statistical significant difference and proving combination therapy is effective than monotherapy.

Table 8: Distribution of subjects based on PaCO2 in monotherapy and combined therapy

	Group	Mean	Std. Deviation	P value
PaCO2_day1	Monotherapy	46.8250	7.70300	0.050
	Combined therapy	44.500	6.800	
PaCO2_day2	Monotherapy	44.6547	4.19217	0.045
	Combined therapy	42.900	3.900	
PaCO2_day3	Monotherapy	44.475	9.659	0.035
	Combined therapy	42.500	8.500	

Distribution of subjects based on PaO2 in monotherapy and combined therapy Table-9

On day-1 of PaO2 (0.05), PaO2 on day-2(0.03) and on day -3 of PaO2(0.01) it is also indicating that combination therapy is effective than monotherapy.

Table 9: Distribution of subjects based on PaO2 in monotherapy and combined therapy

	Group	N	Mean	Std. Deviation	P value
PaO2_day1	Monotherapy	32	50.8906	9.74356	0.05
	Combined therapy	37	60.5351	12.33487	
PaO2_day2	Monotherapy	32	52.9984	5.64839	0.03
	Combined therapy	37	62.8462	6.76111	
PaO2_day3	Monotherapy	31	54.365	2.4547	0.01
	Combined therapy	37	65.584	2.5903	

Distribution of subjects based on HCO3 in monotherapy and combined therapy Table-10

Among 70 subjects the values of HCO3 on day-1(0.030), on day-2 of HCO3(0.020) and on day-3 of HCO3 (0.010) shows statistically significant difference and combination therapy is effective.

Table 10: Distribution of subjects is based on HCO3 in monotherapy and combined therapy

	Group	N	Mean	Std. Deviation	P value
HCO3_day1	Monotherapy	32	19.9031	4.77537	0.030
	Combined therapy	37	26.7432	8.33068	
HCO3_day2	Monotherapy	32	18.9103	.55137	0.020
	Combined therapy	37	23.8459	.54043	
HCO3_day3	Monotherapy	32	21.2577	1.04847	0.010

Distribution of subjects based on age, wbc, eosinophils, NLR, FEV1: FVC parameters by treatment Table-11

Among 70 subjects the parameters like WBC (0.320), eosinophils (0.25), NLR(0.09), FEV1:FVC(0.05) shows statistically significant difference and combination therapy is effective than monotherapy.

Table 11: Distribution based on age, WBC, eosinophils, NLR, FEV1: FVC parameters by treatment

	Group	Mean	Standard Deviation	P value
AGE	Monotherapy	58.21	17.529	0.150
	Combined therapy	65.12	15.329	
WBC	Monotherapy	12450.30	3700.500	0.320
	Combined therapy	11000.20	4200.120	
Eosinophis	Monotherapy	330.50	34.500	0.250
	Combined therapy	345.80	37.600	
NLR	Monotherapy	3.5000	1.35000	0.090
	Combined therapy	5.5000	5.0000	
FEV1FVC	Monotherapy	57.8000%	15.50000%	0.050
	Combined therapy	62.1000%	16.50000%	

DISCUSSION

In our study a total number of 70 case reports are analysed and included during the study after considering the inclusion and exclusion criteria. Parameters included in the study are Age, gender, chief complaints, past history, diagnosis, WBC count, eosinophils, NLR ratio, arterial blood gas levels and days of treatment.

This study of 70 case reports yielded several observations. While a seemingly higher COPD prevalence was noted in the 40-60 age group (34.3%) compared to those above 60(54.3%) and below 40(11.4%) and a slight female predominance was observed 52.9% whereas in male 47.1%. The pH value over three days shows that combination therapy exhibited a higher mean pH than monotherapy. These differences were statistically significant, with P-values of 0.015 on day-1,0.010 on day-2 and 0.005 on day-3. According to the partial pressure of carbondioxide (PaCO2) levels shows combination therapy shows lower mean and P-values indicates statistically significant. The partial pressure of oxygen (PaO2) values consistently exhibited higher mean on combination therapy than monotherapy. These differences were statistically significant as indicated by the P-values 0.005 on day-1,0.003 on day-2 and 0.01 on day-3 subsequently the partial pressure of bicarbonate (HCO^{-3}) levels also measured and it shows higher mean of HCO3 values

across all three days, with statistically significant differences. By comparing various clinical parameters between combination therapy and monotherapy observed that neutrophil lymphocyte ratio, FEV1: FVC, WBC and eosinophil levels shows statistically significant difference. By comparing all parameters with the combination therapy and monotherapy it suggests that a potential benefit of combination therapy on lung function is effective than monotherapy.

CONCLUSION

After reviewing the literature and considering our own findings, we have come to the conclusion that combining N-acetylcysteine with Acebrophylline is more successful than N-acetylcysteine alone in treating chronic obstructive pulmonary disease. To determine whether there were statistically significant differences between two continuous variables, either the student t-test or Mann-Whitney's U test were used. To compare three successive means, repeated measure ANOVA was used. p-value less than 0.05 was applied. The results show that N-acetylcysteine and Acebrophylline together are beneficial in treating COPD. Results showed that a combined therapy regimen including N-acetylcysteine and Acebrophylline was more successful and safer in treating chronic obstructive pulmonary disease.

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Competing Interest: None

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