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Comparison of Clinical Outcomes between Acetylcysteine and Ambroxol in Post Acute Exacerbation of COPD Patients

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ABSTRACT: Literature studies show that the use of acetylcysteine or ambroxol can accelerate improvement of clinical outcomes of post acute exacerbation chronic obstructive pulmonary disease (AECOPD) patients. This study aims to compare the clinical outcomes of acetylcysteine and ambroxol administration in post AECOPD patients. The study was cohort design, prospective, to comparison of clinical outcomes of acetylcysteine and ambroxol with post AECOPD outpatients coming for clinical chekups in August 2023 at Respira Lung Hospital Yogyakarta. Clinical outcomes parameters were observed on day zero and thirty for CAT score and day zero and four for cough score. The patients were categorized into two groups: acetylcysteine group (n=30) and ambroxol group (n=30). There was no significant difference between two groupsto change of CAT score and cough score (p>0.05) post AECOPD. The acetylcysteine group compared to ambroxol, there was a mean decrease in morning cough score-1.10±1.11 vs-0.87±1.12 (p=0.228), night cough score-1.53±1.43 vs-1.13±1.31 (p=0.438), and CAT score-2.43±5.45 vs-2.90±3.41 (p=0.391). Providing additional therapy of acetylcysteine or ambroxol in this study did not significantly reducing cough scores and CAT scores in post AECOPD patients.

Keywords: **acetylcysteine; ambroxol; AECOPD; cat score; cough score.**

Introduction

Chronic obstructive pulmonary disease (COPD) is preventable and treatable respiratory condition marked by a gradual restriction of airflow. This limitation is linked to a heightened chronic inflammatory response within the airways and lungs, triggered by exposure to gases or harmful particles. The severity of the disease in patients is influenced by exacerbations and the presence of comorbidities [1].

According to data from the World Health Organization (WHO) in 2002, COPD ranked as the fifth leading cause of death globally. Projections indicate that by 2030, it is expected to become the third leading cause of death worldwide, following cardiovascular disease and cancer [2]. Riskesda data from 2013 suggests that the prevalence of COPD in Indonesia is approximately 3.7% of the total population, while in Yogyakarta (DIY), it accounts for about 3.1% of the local population [3]. This prevalence may rise with the growing number of smokers, considering that 90% of COPD patients have a history of smoking. The association between smoking and COPD demonstrates a dose-response relationship, where a higher number of cigarettes smoked and prolonged smoking habits correspond to an increased risk of developing COPD [2].

Exacerbations are usually triggered by infection or air pollution with clinical symptoms of shortness of breath, cough, increased sputum production, and sputum discoloration [2]. Exacerbations indicate a worse disease prognosis and greatly impact the patient's quality of life [4]. While most treatments for COPD have not demonstrated a significant impact on improving survival or slowing the progressive decline in lung function, several therapies do enhance lung function, enhance quality of life, and mitigate the risk of acute exacerbations chronic obstructive pulmonary disease (AECOPD) as well as reduce hospitalization duration. Mucolytic therapy is one such intervention that falls into this category [5].

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2022 guidelines suggest the routine use of mucolytic agents, as they have the potential to decrease exacerbations of COPD and modestly enhance quality of life, particularly in

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patients who are not using inhaled corticosteroids [6]. Certain mucolytic agents can influence mucus production and decrease its viscosity, facilitating easier expectoration of sputum. This, in turn, lowers the risk of infection and contributes to an improvement in overall quality of life. Presently, various mucolytic agents have been developed, though their effectiveness in preventing acute exacerbations and enhancing quality of life shows varying outcomes [7].

Studies show that acetylcysteine exhibits antioxidant and anti-inflammatory properties, leading to a substantial reduction in the risk of exacerbations and an improvement in the quality of life for individuals with moderate and severe COPD [7]. AECOPD patients who received additional acetylcysteine therapy experienced significantly and consistently fewer exacerbations than those without administration. Administration of high-dose acetylcysteine >600 mg per day to prevent exacerbations [8]. In addition, acetylcysteine administration improved partial pressure of carbon dioxide (PaO2), partial pressure of carbon dioxide (PaCO2), saturation oxigen (SaO2) significantly compared with no acetylcysteine administration. There was also significant improvement in clinical signs, including wheezing, dyspnea, and the need for ventilator oxygen support [9].

Long-term use of ambroxol versus placebo did not provide a significant difference in preventing AECOPD patients. Nevertheless, in individuals experiencing more pronounced respiratory symptoms than previously, a notable distinction in the cumulative persistence of exacerbation-free periods was observed between those treated with ambroxol and those receiving a placebo. This suggests that ambroxol administration is more beneficial in COPD patients who are experiencing an exacerbation [10]. The evaluation of various journal reviews on the efficacy and safety of ambroxol in the treatment of airway disease led to the conclusion that the benefit-to-risk profile of ambroxol is established in adult patients. It demonstrates effectiveness in alleviating respiratory symptoms and preventing acute exacerbations [11].

The difference in therapeutic effects between acetylcysteine and ambroxol is the reason for the need for data related to the comparison of clinical outcomes of the use of these two drugs in accelerating post acute exacerbation improvement so that it can be taken into consideration in planning drug procurement in hospitals.

Assessment of the patient's health-related quality of life allows clinicians to make individualized patient management decisions. GOLD recommends the COPD Assessment Test (CAT) as a quality of life assessment measure in COPD patients because it is simple and provides comprehensive coverage of the impact of COPD on patients' well-being [6,12].

The cough score is used to measure daily symptoms as an indicator of cough severity against the cough frequency filled in by the patient himself. Daily symptom scores of cough severity were measured during the day and night in order to determine the effectiveness of the additional mucolytic therapy given [13].

Methods

Research Method

The research used a prospective cohort design that assessed the comparison of clinical outcomes of acetylcysteine and ambroxol administration in post AECOPD outpatients at Respira Lung Hospital coming for clinical checkups in August 2023. Sampling in this study used consecutive sampling method. The subjects were categorized into two groups: acetylcysteine group (n=30) and ambroxol group (n=30). Clinical outcome monitoring was performed on CAT score on day 0 and day 30, cough score on day 0 and day 4. All therapy monitoring utilized the direct patient interview method. The research was conducted for 2 months during August to September.

All patients included were males and females above 18 years of age, post AECOPD who received standard therapy according to the degree of COPD (grade A: bronchodilator SABA or SAMA, grade B: LABA or LAMA, grade C: LAMA, grade D: LAMA, or LAMA+LABA, or ICS+LABA)) and prepared to take part in the research after completing the informed permission form, getting one of the mucolytic therapies of acystylcysteine or ambroxol. Exclusion criteria were patients with lung cancer, active pulmonary tuberculosis, liver disease, kidney disease, and psychiatric disorders.

CAT score measurements were taken on day 30 after treatment because quality of life assessment is related to long-term measurements after treatment. Re-measurement of CAT score is one of the recommended parameters in COPD patients post-hospitalization due to exacerbation, measurements are recommended at 1-4 weeks and 12-16 weeks post-hospitalization. Exacerbation recovery time varies from 4-6 weeks [6]. while the measurement of cough scores to assess the effectiveness of drug therapy which is symptomatic in nature so that measurements are taken immediately after the drug has been taken, which is around 4 days.

Research Instrument

The CAT questionnaire is a validated, short and simple tool to monitor the effect of treatment on quality of life. In Indonesia, the CAT questionnaire has been validated in the Ngaglik Sleman area. The results of the CAT questionnaire validity test are total item correlation = 0.25, r count =>0.8, and Cronbach α reliability =>0.600 [14]. The CAT score consists of 8 points of symptom parameters with a score of 0-5 per parameter, the increase in score indicates the higher the severity affecting the patient's quality of life. The higher the score, the more severe the symptoms.

Cough score questionnaire as a tool to monitor the effect of treatment on cough frequency, cough measured during the day and night. The results of the cough questionnaire validity test were total item correlation = 0.52 r count = 0.24, and Cronbach α reliability = 0.51-0.88 [15]. The cough score is an evaluation conducted to assess cough and its response to treatment, primarily relying on subjective symptom perception. It involves the use of a cough visual analog scale (VAS) score, measured both during the day and night [16]. The cough score consists of 6 points with each cough symptom scored 0-5. The higher the score, the more severe the symptoms.

An informed consent form served as evidence of consent to follow and respond to questions from researchers. Data collection sheets were used to gather information from patients with a diagnosis of COPD, including demographics, compliance level, comorbid diseases, severity of illness, smoking history, combination of prescribed drugs obtained from patient medical records, and information from patient interviews.

Research Procedure

This research has received an ethical clearance from Respira Lung Hospital with number 019/KEPK/VII/2023. The questionnaire have be tested for validity at a Public Professional Center.

Data Analysis

Analysis related to the effectiveness of using COPD adjunctive therapy post acute exacerbation using the mucolytic acetylcysteine compared to ambroxol was carried out using instruments to assess cough scores and CAT scores. Scoring was done by researchers based on the results of interviews with patients using cough score instruments and CAT scores. All quantitative data are presented as mean±SD. Data processing was carried out statistical analysis by IBM SPSS Statistic versi 26. The analysis method used in this study for analysis baseline characteristic uses kruskal wallis test and chi suare test, and for analysis clinical outcome using the mucolytic acetylcysteine compared to ambroxol uses the Independent T test (if the data is normally distributed) or Mann Whitney (if the data is not normally distributed).

Result and Discussion

The baseline characteristics of the subjects observed in this study were age, gender, smoking status, medication compliance. In addition, comorbid diseases (diabetes, hypertension, cardivascular disease, neurological disease) were also observed, as well as other pharmacological therapies obtained by patients during treatment at the pulmonary polyclinic (oral bronchodilators, oral corticosteroids, SABA inhalation, LABA inhalation, SAMA inhalation, LAMA inhalation, antibiotics). The baseline characteristics of patients can be seen in table 1.

There was no significant difference in the baseline characteristics of the study subjects (table 1) between the acetylcysteine group and the ambroxol group (p>0,05), so that the two groups had the same or comparable conditions and some of these baseline characteristics did not affect the ability of acetylcysteine and ambroxol in reducing the cough of the study subjects. Except for the percentage of comorbid hypertension. In the acetylcysteine group, the proportion of comorbid hypertension was greater than the ambroxol group (p value 0,037).

Age is a risk factor for COPD that cannot be modified, but increasing age increases the risk of COPD, especially at the age of over 40 years because there is a decrease in lung function compared to young adults [17,18]. This statement aligns with the findings of this study, indicating that there was no significant difference in the average age of COPD patients between the two groups, namely 63,22 ± 8,53 years (p = 1,000).

Gender is one of the non-modifiable risk factors for COPD [19]. In this study, the distribution of gender between the two groups was not significantly different (p=0,426) with a greater percentage of male patients compared to female patients. Based on Riskeda 2018 COPD occurs mostly in men due to increased tobacco use, about 60% of the male population in Indonesia are smokers [20].

Smoking status is closely related to the impact of COPD in the future, smoking is the biggest risk factor that can cause COPD, the longer the duration of a person smoking, the higher the risk of developing COPD [21,22]. The risk of COPD in individuals who have quit smoking diminishes as the duration of smoking cessation

Table 1. Baseline characteristics of the study participants of the study

Charcteristics	n=60	Groups		*p-value*
		Acetylcysteine (n=30)	Ambroxol (n=30)	
Mean age (years)	63,22±8,53	63,2±7,09	63,23±9,77	[a]1,000
Gender (n [%])				
Male	37 [61,67]	20 [66,67]	17 [56,67]	[b]0,426
Female	23 [38,33]	10 [33,33]	13 [43,33]	
Smoking status(n [%])				
Smokers	2 [3,33]	2 [6,67]	0 [0]	[b]0,364
Ex-smokers	26 [43,33]	13 [43,33]	13 [43,33]	
Non smokers	32 [53,33]	15 [50]	17 [56,67]	
Compliance (n [%])				
Non compliance	5 [8,33]	2 [6,67]	3 [10]	[b]0,640
Compliance	55 [91,67]	28 [93,33]	27 [90]	
Comorbid Diabetes (n [%])				
Yes	1 [1,67]	1 [3,33]	0 [0]	[b]0,313
No.	59 [98,33]	29 [0,97]	30 [100]	
Comorbid HT (n [%])				
Yes	26 [43,33]	17 [56,67]	9 [30]	[b]0,037*
No.	34 [56,67]	13 [43,33]	21 [70]	
Comorbid CVD (n [%])				
Yes	18 [30]	7 [23,33]	11 [36,67]	[b]0,260
No.	42 [70]	23 [76,67]	19 [63,33]	
Comorbid ND (n [%])				
Yes	5 [8,33]	3 [10]	2 [6,67]	[b]1,000
No.	55 [91,67]	27 [90]	28 [93,33]	
Other drugs during hospital control				
Oral bronchodilators (n [%])				
Yes	24 [40]	12 [40]	12 [40]	[b]1,000
No.	36 [60]	18 [60]	18 [60]	
Oral Corticosteroids (n [%])				
Yes	14 [23,33]	8 [26,67]	6 [20]	[b]0,542
No.	46 [76,67]	22 [73,33]	24 [80]	
SABA Inhalation (n [%])				
Yes	39 [65]	20 [66,67]	19 [63,33]	[b]0,787
No.	21 [35]	10 [33,33]	11 [36,67]	
LABA Inhalation (n [%])				
Yes	51 [85]	26 [86,67]	25 [83,33]	[b]0,488
No.	9 [15]	4 [13,33]	5 [16,67]	
SAMA Inhalation (n [%])				
Yes	34 [56,67]	17 [56,67]	17 [56,67]	[b]1,000
No.	26 [43,33]	13 [43,33]	13 [43,33]	
LAMA Inhalation (n [%])				
Yes	45 [75]	22 [73,33]	23 [76,67]	[b]0,766
No	15 [25]	8 [26,67]	7 [23,33]	
Oral Antibiotics (n [%])				
Yes	4 [6,67]	2 [6,67]	2 [6,67]	[b]1,000
No.	56 [93,33]	28 [93,33]	28 [93,33]	

[a]Kruskal Wallis Test; [b]Chi Square Test; *There was significant, CVD= Cardiovaskular Disease; HT= Hypertension; n= number of patients; ND= Neurogical Disease; LABA= Long Acting Beta Agonist; LAMA= Long Acting Muscarinic Antagonist; SABA= Short Acting Beta Agonist; SAMA= Short Acting Muscarinic Antagonist.

increases [23]. In this study, the distribution of smoking status between the two groups did not exhibit a significant difference (p=0.364), with the percentage of patients categorized as smokers, ex-smokers, and non-smokers being 3.33%, 43.33%, and 53.33%, respectively.

The occurrence of comorbid conditions, including diabetes, hypertension, cardiovascular disease, and nervous system disorders, was observed to be relatively low in both groups, except for hypertension (43.33%) and cardiovascular disease (30%). Hypertension and cardiovascular disease emerge as the most prevalent comorbid conditions in individuals diagnosed with COPD. Hypertension stands out as the predominant condition in the global population, with an adult prevalence of 31.1%. Notably, hypertension has been identified as a significant risk factor for cardiovascular disease and frequently appears as a comorbid condition alongside COPD. Approximately 17% of hospitalized COPD patients suffer from hypertension [24]. COPD patients have a significantly higher prevalence of cardiovascular disease than patients without COPD (59.6% vs 28.4%). COPD and cardiovascular disease generally coexist and interact with each other. The worsening of cardiovascular disease is one of the triggering factors for COPD exacerbations, while COPD exacerbations trigger cardiovascular worsening, even resulting in heart muscle cell death [25]. In COPD patients who experience acute exacerbations, there is an increase in troponin which can cause cardiac stress, resulting in cardiac events during or post acute exacerbations [26].

The administration of corticosteroid therapy and bronchodilators in both oral and inhaled forms is the main therapy for COPD, which is given depending on the severity of COPD [6]. Bronchodilator medications play a crucial role in maintaining open airways and may reduce the accumulation of mucus in the lungs [27]. In acute exacerbation conditions, the administration of SABA bronchodilators is more recommended because of its rapid action, and systemic corticosteroid administration in exacerbation conditions can accelerate recovery, improve lung function (FEV1) and conditions of arterial hypoxemia. While the administration of antibiotics in exacerbations can be adjusted to the germ pattern of the local hospital, but empirical antibiotics commonly used are one of the macrolides (azithromycin) [2].

Analysis related to the effectiveness of using COPD adjunctive therapy post acute exacerbation using the mucolytic acetylcysteine compared to ambroxol was carried out using instruments to assess cough scores and CAT scores. Scoring was done by researchers based on the results of interviews with patients using cough score instruments and CAT scores.

In several COPD studies and guidelines, the administration of mucolytics has different effectiveness

Table 2. Result comparison cough scoring of acetylcystein groups and ambroxol group in post AECOPD pasients

Variables	Groups				*p-value*
	Acetylcysteine (n=30)		Ambroxol (n=30)		
	Mean±SD	Min-Max	Mean±SD	Min-Max	
Morning Cough Score					
Before treatment (Day 0)	1,83±1,34	0-4	1,77±1,26	0-4	[a]0,820
After Treatment (Day 4)	2,10±1,33	0-3	1,91±1,35	0-4	[a]0,685
p-value	[a]0,000*		[a]0,001*		
Night Cough Score					
Before treatment (Day 0)	2,10±1,33	0-4	1,91±1,35	0-4	[a]0,706
After Treatment (Day 4)	0,57±0,62	0-2	0,83±1,00	0-4	[a]0,009*
p-value	[a]0,000*		[a]0,107*		
Difference in Decrease of Cough Score					
Morning Cough Score	-1,10±1,11	+2-(-3)	-0,87±1,12	+1-(-4)	[a]0,228
Night Cough Score	-1,53±1,43	0-(-4)	-1,13±1,31	+2-(-4)	[a]0,438

[a]Mann Whitney Test; *There was significant; Max= Maximal score; Min= Minimal score; SD= Standard deviation; n= number of patients

data when given to patients with acute COPD exacerbations. The meta-analysis study showed that the administration of mucolytics as adjunctive therapy is beneficial in preventing COPD exacerbations in patients who experience frequent exacerbations, The efficacy of mucolytics remains consistent regardless of the severity of COPD and the utilization of inhaled corticosteroids [8]. Other studies suggest that the administration of mucolytics may be beneficial in reducing the formation of sputum discharge. Nevertheless, it does not exert a substantial influence on the quality of life and lung function of individuals who use it [28].

COPD exacerbations are acute episodes of respiratory symptoms that worsen persistently beyond normal daily variations. Such episodes are associated with impaired quality of life, accelerated decline in lung function. Increased cough and/or sputum volume are common symptoms of COPD exacerbation [29,30]. Mucolytics enhance mucociliary clearance and promote the expulsion of phlegm by altering the degree of cross-linking and molecular interactions within mucin polymers. This in turn, regulates the viscoelastic properties of phlegm [31]. According to a meta-analysis review, individuals with COPD exacerbations who used mucolytics experienced a 37% increase in treatment success and improvements in symptoms that were clinically significant. Moreover, mucolytics lessen cough and ease sputum production [32].

Table 2 shows a comparison of the average cough score values in each acetylcysteine group and ambroxol group, which were assessed on day 0 or when the patient was in control and had not received therapy, and day 4 after therapy.. Based on the assessment of morning and night cough scores conducted before and after therapy, it was found that the mean difference in cough scores on acetylcysteine was greater than ambroxol. After statistical analysis, the results were not significantly different in the difference in morning cough scores (p=0.228) or night cough scores (p=0.438), meaning that the effect of acetylcysteine and ambroxol therapy was the same in reducing patient cough scores. However, the standard deviation of the difference in mean cough scores in this study is large, indicating that the data is spread over a wide range and large variations in data.

A randomized double-blind study in subjects with acute exacerbation of COPD showed that cough VAS scores were significantly different between groups receiving acetylcysteine compared to groups not receiving acetylcysteine (p<0,05) [7]. Meanwhile, there was no significant difference in scores between the group that received ambroxol compared to the group that did not receive ambroxol (p>0,05), but it was lower than before the therapy [33]. This was also seen in the results of this study, on the 4th day of mucolytic therapy, the average morning cough score and night cough score decreased compared to before the administration of mucolytic drugs.

Table 3 shows a comparison of the average CAT score values in each acetylcysteine group and ambroxol group, which were assessed on day 0 or when the patient was in control and had not received therapy, and day 30 after therapy. Based on the assessment of CAT scores carried out before and after the administration of therapy, it was found that the mean difference in CAT scores on acetylcysteine was greater than ambroxol, After statistical analysis, the results were not significantly different (p = 0.391) in the difference in CAT scores, meaning that the effect of acetylcysteine and ambroxol therapy was the same in reducing the patient's CAT score. However, the standard deviation of the difference in mean CAT scores in this study is large, indicating that the data is spread over a wide range and large variations in data.

Table 3. Result CAT score of acetylcystein groups and ambroxol group in post AECOPD pasients

Variables	Groups				p-value
	Acetylcysteine (n=30)		Ambroxol (n=30)		
	Mean±SD	Min-Max	Mean±SD	Min-Max	
CAT Score					
Before treatment (Day 0)	13,33±6,71	5-28	14,77±4,54	8-29	[a]0,685
After treatment (Day 30)	10,90±4,82	4-23	11,87±4,06	5-23	[b]0,412
p-value	[a]0,023*		[a]0,023*		
Different in Decrease of CAT score					
CAT score	-2,43±5,45	(-18)-9	-2,90±3,41	(-11)-7	[b]0,391

[a]Mann Whitney Test; [b]Independent T Test; *There was significant Max= Maximal score; Min= Minimal score; SD= Standard deviation; n= number of patients

A randomized double-blind study on subjects with acute exacerbation of COPD showed that CAT scores were significantly different between groups receiving acetylcysteine compared to groups not receiving acetylcysteine (p<0,05) [7]. Another study showed CAT scores were not significantly different between groups receiving acetylcysteine compared to groups not receiving acetylcysteine (p=0,833) [34]. Meanwhile, there was no significant difference in CAT score between the group receiving ambroxol compared to the group not receiving ambroxol (P>0.05), but it was lower than before therapy [33]. This was also seen in the results of this study, on the 30th day of mucolytic therapy, the mean CAT score decreased compared to before the administration of mucolytic drugs.

Clinical outcomes in post-acute exacerbation COPD patients in the form of cough scores and CAT scores may be influenced by the basic characteristics of the subjects which can be confounding variables. Therefore, further analysis was conducted to see the influence of confounding variables on clinical outcomes including age, gender, smoking history, patient compliance, comorbid diseases, and the last drug combination received by the patient. The analytical method used when the dependent variable was numeric (cough and CAT scores) was linear regression [35].

Based on the results of linear regression analysis which can be seen in table 4, it shows the influence of confounding variables in influencing clinical outcomes in the study subjects. In the morning cough score, the effect of confounding variables on the morning cough score was 46%, the confounding variables that had a significant effect (p<0.05) on the morning cough score were smoking status, medication compliance, comorbid diabetes, cardiovascular disease, and administration of other drugs in the form of bronchodilators. Meanwhile, the night cough score and CAT score showed that none of the confounding variables had a significant effect (p>0.05) on the night cough score and CAT score.

Smoking status is closely related to the impact of COPD, smoking is the biggest risk factor that can lead to COPD [21,22]. The presence of cough and mucus affects patients' quality of life, and smoking cessation was identified as the decisive inflection point for cough

Table 4. Analysis compounding factor in clinical outcome

Compounding factor	Coefficient Regretion *p-value* (sig.)			R^2		
CI [95%]	**Morning cough score**	**Night cough score**	**CAT score**	**Morning cough score**	**Night cough score**	**CAT score**
Age	0,509	0,649	0,875			
Gender	0,786	0,093	0,171			
Smoking status	***0,034**	0,498	0,376			
Compliance	***0,012**	0,412	0,267			
Comorbid disease Index						
Diabetes	***0,015**	0,400	0,834			
HT	0,192	0,753	0,106			
CVD	***0,003**	0,290	0,550			
ND	0,862	0,601	0,275	0,460	0,274	0,177
Other drugs combination						
Bronchodilator Oral	***0,044**	0,465	0,873			
Coticosteroid Oral	0,616	0,048	0,875			
Antibiotic	0,135	0,755	0,877			
SABA Inhalation	0,751	0,697	0,891			
LABA Inhalation	0,625	0,754	0,477			
SAMA Inhalation	0,717	0,162	0,865			
LAMA Inhalation	0,808	0,238	0,880			

*There was significant; CVD= *Cardiovaskular Disease*; ND= *Neurogical Disease*; HT= Hipertensi; SABA= *Short Acting Beta Agonist*; LABA= *Long Acting Beta Agonist*; SAMA= *Short Acting Muscarinic Antagonist*; LAMA= *Long Acting Muscarinic Antagonist*

and mucus [36]. Medication adherence is one of the most important factors that enable successful treatment of COPD, medication non-adherence is consistent with the failure of a therapy [37]. High patient compliance in using mucolytics increases the success of therapy [31].

Presence of comorbid diabetes and cardiovascular disease. COPD patients have a significantly higher prevalence of cardiovascular disease than patients without COPD (59.6% vs 28.4%). COPD and cardiovascular disease commonly coexist and interact with each other. The worsening of cardiovascular disease is one of the triggering factors for COPD exacerbations, while COPD exacerbations trigger cardiovascular worsening, even resulting in heart muscle cell death [25]. In COPD patients who experience acute exacerbations, there is an increase in troponin, which can cause cardiac stress, leading to cardiac events during or after acute exacerbations [26]. One of the signs of exacerbation is coughing, which can affect the cough score.

The use of oral bronchodilators directly affects coughing. However, in some studies the use of oral bronchodilators is given to reduce symptoms such as coughing, wheezing, and shortness of breath. The use of oral bronchodilators can improve lung function and blood oxygen and carbon dioxide levels. Bronchodilator medications help keep the airways open and can decrease the amount of mucus in the lungs [27].

Limitation

This study has several limitations that may affect the results in this study, including: although baseline characteristics and several confounding variables have been controlled so that the two sample groups are considered comparable, the total sample is still not optimal enough regarding representation of all post-exacerbation COPD patients. There are several uncontrollable factors that may interfere with the results of the study such as exposure to pollution in the work and living environment, changeable weather, and physical activity of patients. The amount of medication given to patients was different, acetylcysteine was given 10 tablets with the rule of use 2-3 times a day which means it runs out within 3 days if taken every day. Meanwhile, ambroxol was given 20 tablets with a rule of use 3 times a day which means it runs out in 6-7 days if taken every day. CAT score measurement was done after 30 days of therapy so that the CAT score could be affected by the duration of medication.

Conclusion

There was a difference in the decrease in CAT score and cough score between the two groups of additional mucolytic therapy, where the mean difference in the decrease in CAT score of ambroxol was greater than that of acetylcysteine group. Meanwhile no significant difference in CAT score difference between acetylcysteine and ambroxol groups (p=0.391), difference in morning cough score (p=0.228), and night cough score (p=0.438). There are several confounding variables that may affect the cough score results including smoking status, medication adherence, comorbid diabetes, cardiovascular disease, and administration of other drugs such as bronchodilators.

Conflict of Interest

The authors have no conflicts of interest regarding this investigation.

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