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Study of the Bronchoreversibility and Outcomes in Patients with Chronic Obstructive Pulmonary Disease (COPD)

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ABSTRACT

Background: acute bronchial reversibility after inhalation of short acting Beta2 agonists (SABA) has been traditionally used to differentiate asthma from chronic obstructive pulmonary disease. However, it is clear that a positive reversibility test does not exclude the diagnosis of chronic obstructive pulmonary disease. About 24% of patients with COPD met the criteria for reversibility. **Aim of the Work:** assessment of airflow reversibility & outcomes in patients with COPD. **Patients and Methods:** this study was conducted at Chest Department, Al-Hussein Hospital, Al-Azhar University and the Chest Hospital in Addakahliah Governorate in the period between January & December 2017. The study included 30 patients with COPD; diagnosed and classified according to [Global initiative for chronic Obstructive Lung Disease (GOLD), 2017]. **Results:** mean PFT (FEV1, FEV1 / Pred. FVC % and PEFR) showed no statistically difference pre and post BDT. There was highly statistically significant difference in PFTs (FEV1, FEV1 / Pred. FVC % and PEFR) at 4, 6 and 8 weeks compared to Pre BDT. A highly statistically significant improvement in ABG (PaO2, PaCO2 and pH) was found through weeks of study compared to baseline ABG. CAT test results showed highly significant improvement after 8 weeks compared to 0 week. **Conclusion:** bronchoreversibility is not determined from the first session of nebulizer. Moreover, mostly there is no difference in pulmonary functions mainly forced expiratory volume in the first second between pre and post bronchodilator inhalation. To judge if there is airflow reversibility or not, we must give the patient complete course of treatment for at least one month. Therefore, the lack of acute response to short acting Beta2 agonists does not preclude the beneficial long-term response maintenance bronchodilator treatment.

Keywords: Bronchoreversibility, Outcomes and Chronic Obstructive Pulmonary Disease.

INTRODUCTION

COPD is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases [(1,2)]. COPD is a debilitating disease associated with repeated respiratory events (exacerbation, emergency room visit, hospital or ICU admission) or death [(3)]. Acute bronchial reversibility after inhalation of SABA has been traditionally used to differentiate asthma from COPD. However, it is clear that a positive reversibility test does not exclude the diagnosis of COPD. About 24% of patients with COPD met the criteria for reversibility. Also, the bronchodilator status (positive or negative) varied temporally and did not differentiate clinically relevant outcomes [(4)]. Bronchodilators and anti-inflammatory agents are used to reverse the bronchoconstriction, improve lung function, improve quality of life, improve exercise capacity and prevent exacerbation [(5)]. There is a little information about bronchoreversibility of COPD and its roles in diagnosis in Egypt. Therefore, further researches are required.

AIM OF THE WORK

This work was designed to assess the airflow reversibility & outcomes in patients with COPD after two months of follow up with regular course of treatment mainly by bronchodilators, muscarinic antagonists & corticosteroids.

PATIENTS AND METHODS

This study was conducted at Chest Department, Al-Hussein Hospital, Al-Azhar University and the Chest Hospital in Dekerness, Addakahliah Governorate in the period between January & June 2017. The study included thirty (30) patients with COPD; diagnosed and classified according to (GOLD, 2017) [(2)]. **Ethical approval:** Informed consent was obtained from all patients enrolled in the study after explanation of the aim and method of the research. Ethics Committee in Al-Azhar University approved the study. All patients are in stable or after exacerbation state without significant co-morbidity. There were no risks on patients. **Target population:** Smokers or ex-smokers (considering the smoking is a risk factor), those having COPD > 2 years and co-operative patients were included in the study.

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While pregnant & lactating women, uncontrolled systemic diseases rather than COPD (co morbidity), hypersensitive to any bronchodilators or corticosteroids, receiving Beta-blockers in the last month, handicapped, patients unable to perform the required tests, patients with asthma or malignancy, patients nonresident in the region due to difficulties in follow up and very severe cases that need urgent ICU, all were excluded. **All patients underwent the following:** 1. Full history taking with stress on; family, occupational, environmental, educational, habitual (smoking) and past medical or surgical treatment. 2. Complete clinical examination (general & local). 3. Plain CXR (PA & lateral views). 4. Measuring the pulmonary functions; (FEV_1, FVC and PEFR) before the bronchodilator & 20 minutes after a session of nebulizer with {1ml (5 mg) salbutamol + 2ml saline 0.9%}. 5. Measuring the pulmonary functions; (FEV_1, FVC or PEFR) every two weeks for the following two months and at any respiratory events. 6. ABG on start and every two weeks for the following two months and at any respiratory events. Pulse oximetry used to evaluate a patient's SaO_2 at room air or 20 minutes after the session of nebulizer and need for supplemental oxygen therapy if needed. Blood samples (5ml) were collected from each subject by arterial puncture with a syringe. The blood was not allowed to clot by using heparin and the result was read soon. Blood samples were collected from each patient at room air or 20 minutes after the session of nebulizer. All patients received regular treatment consisted of mainly inhaled; LABA (Formoterol 12 mcg twice daily), LAMA (Tiotropium bromide 18 mcg once daily) and ICS (Beclomethasone 50 mcg twice daily). Outcomes (CATest score was used to evaluate outcomes) were evaluated at the start and the end of the two months. **Statistical analysis**: The collected data were coded, processed and analyzed using SPSS (Version 16) for windows7. The appropriate statistical test was used when needed. P value ≤ 0.05 was considered statistically significant.

RESULTS

Mean age of the studied group was 65.5 years old, most of them were males (80%) while 20% were females and majority of them were smokers (36.7%), ex-smokers (26.7%), non-smokers (23.3%) and passive smokers (13.3%) as shown in table (1). Mean PFT (FEV_1, FEV_1 / Pred. FVC % and PEFR) showed no statistically difference pre and post BDT (table 2). There was highly statistically significant difference in PFTs (FEV_1, FEV_1 / Pred. FVC % and PEFR) at 4, 6 and 8 weeks compared to Pre BDT as shown in table (3)and figures (1&2). A highly statistically significant improvement in ABG (PaO_2, $PaCO_2$ and pH) was found through weeks of study compared to baseline ABG (Table 4 and Fig. 3 & 4). CAT test results showed highly significant improvement after 8 weeks compared to 0 week (Table 5).

Table (1): Demographical data of studied patients

Characteristics	N (%)
Mean age	65.5 y
Sex	
Male	24 (80%)
Female	6 (20%)
Smoking status	
Smoker	11 (36.7%)
Ex-Smoker	8 (26.7%)
Passive Smoker	4 (13.3%)
Non-Smoker	7 (23.3%)

Table (2): Bronchoreversibility among studied group

Item \ PET	Mean FEV_1 (L)		Mean FEV_1 / Pred. FVC (%)	Mean PEFR (L/min.)	
	Act.	Pred.%		Act.	Pred.%
Pre bronchodilator	1.59	55.76	44.66	210.87	46.55
Post bronchodilator	1.61	56.37	45.17	212.8	47.04
Difference	0.02	0.61	0.51	1.93	0.49
P value	0.214		0.313	0.065	

N.B.: Normal FEV_1 / Pred. FVC = 82 %.

Table (3): Statistical analysis of PFTs (FEV_1, FEV_1 / Pred. FVC % and PEFR) through the weeks

PET \ Weeks		Pre	Post	2 Weeks	4 Weeks	6 Weeks	8 Weeks	Difference between pre & 8 weeks	P value
FEV_1 (L)	**Mean**	1.59	1.61	1.62	1.87*	1.9*	2.02*	0.41	≤0.0001
	pred.%	55.7	56.3	56.74	65.76	68.36	70.86	15.1	
	Range	1-2.7	1-2.88	1.04 - 2.93	1.06 - 2.99	1.03 - 3.10	1.16 - 3.03	-	
FEV_1 / Pred. FVC (%)	**Mean**	44.6	45.1	45.47	52.52*	54.62*	56.90*	12.24	≤0.0001
	Range	30.6- 64	35.3- 68	37.14-74.39	37.26-70.85	39.49-73.45	41.83-71.8	-	
PEFR (l/min)	**Mean**	210	212	214.4	257.7	268.4*	283.3*	72.5	≤0.0001
	pred.%	46.5	47.0	47.53	56.8	58.43	62.46	15.91	
	Range	100-327	120-351	103- 365	129- 361	156- 364	170- 383	-	

N.B.:* means statistically significant difference compared to pre bronchodilator.

Table (4): Statistical analysis of ABG (PaO_2, $PaCO_2$ and pH) through the weeks

ABG \ Weeks		0 Week	2 Weeks	4 Weeks	6 Weeks	8 Weeks	Difference between pre & 8 weeks	P value
PaO_2 (mmHg)	**Range**	51– 78	52 - 75	63 – 80	63 - 83	62 - 88	-	≤ 0.0001
	Mean	63.06	66.20	69.46*	73.3*	76.2*	13.13	
$PaCO_2$ (mmHg)	**Range**	35– 69	36 - 59	38 – 69	35 - 53	38 - 49	-	≤ 0.0001
	Mean	52.1	47.86	46.33	43.9*	42.6*	9.5	
pH	**Range**	7.3 - 7.44	7.3 - 7.43	7.32 - 7.44	7.32 - 7.45	7.33 - 7.45	-	≤ 0.0001
	Mean	7.346	7.346	7.363	7.369*	7.372*	0.026	

N.B.:* means statistically significant difference compared to 0 week.

Table (5): Statistical analysis of Outcomes (CATest) at 0 & 8 weeks

Number / CAT	0 week	Mean score	8 weeks	Mean score	P value
Very high	13(43.3)	32.84	_	_	≤ 0.0001
High	17(56.7)	28.29	11(36.7)	27	
Moderate	_	_	14(46.7)	15.5	
Low	_	_	5(16.7)	7.6	

N.B.: classified according to their mean score: ● Very High: 30 - 40 ● High: 20 - 30 ● Moderate: 10 - 20 ● Low: 0 - 10.

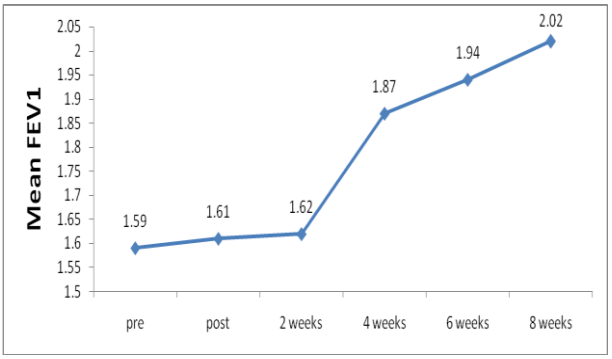

Fig. (1): Shows increasing mean FEV_1 through weeks of the present study.

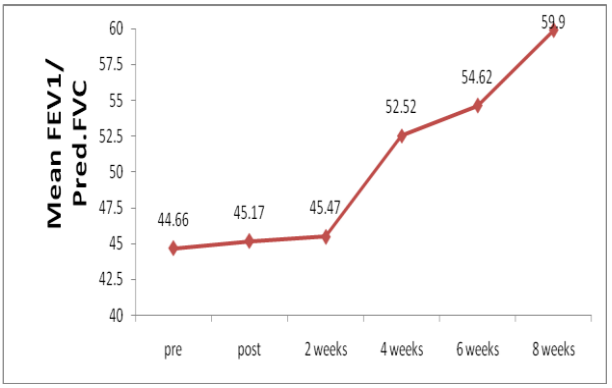

Fig. (2): Shows increasing mean FEV_1 / pred. FVC % through weeks of the study.

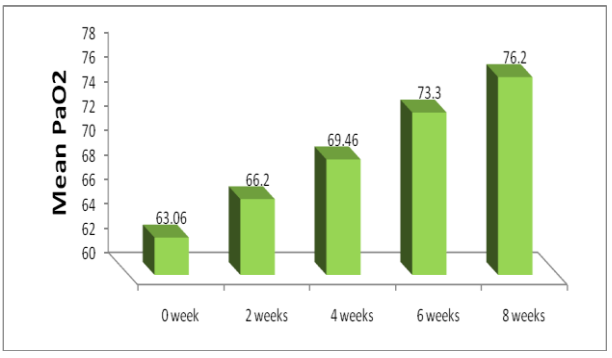

Fig. (3): Shows increasing mean PaO_2 through weeks of the present study.

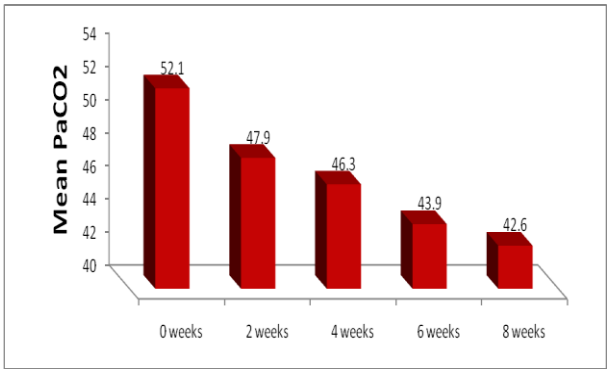

Fig. (4): Shows decreasing mean $PaCO_2$ through weeks of the present study.

DISCUSSION

Most of the information available on COPD incidence, prevalence, morbidities and mortalities come from high income countries. Even in those countries, accurate epidemiologic data on COPD are difficult and expensive to collect. In the next 10 years, the total deaths from COPD are projected to increase by more than 30% unless urgent action is taken to reduce the underlying risk factors especially tobacco use. The acute bronchial reversibility after inhalation of SABA has traditionally used to differentiate asthma from COPD. However, it is clear that a positive reversibility test did not exclude the diagnosis of COPD [(1)]. 24% of patients with COPD met the criteria of broncho-reversibility [(3)]. Also, the bronchoreversibility status (positive or negative) varied temporally and did not differentiate clinically relevant outcomes [(4)]. The mean age of the patients in the present study was 65.5 years old (ranged between 42-82 years). This confirms that COPD is a progressive disease affecting the middle and old ages but is more common in old ages (53.3% of the patients between 60-70 years old). Nearly the same observation was reported by ***Sitkauskiene et al.*** [(6)] who showed 64 years old in a study of 38 patients with COPD. Also, ***Hanania et al.*** [(7)] reported 63 years old in a study of 544 Patients with the same disease and ***Marin et al.*** [(8)] reported 63 years old in a study of airflow reversibility and long term outcomes in 1203 COPD patients. 24 male patients were included in the present study represent 80% and 6 females who represent 20%. According to this sample size of people in the community, COPD is common in males more than in females. The same incidence of males to females (20.3% for females) was reported by ***Hanania et al.*** [(7)] in a study of 544 patients with COPD randomly

selected at 17 clinics. ***WHO*** [9] stated that COPD now affects men and women almost equally due to increased tobacco use in both sexes. The difference of incidence in females with COPD in the present study and the WHO statement is based on the fact that in the Middle East countries, the social view for smoking in females is still refused. In the current study, 11 patients out of 30 patients were still smokers (36%), while 8 patients were ex-smokers (26.7%). ***Marin et al.*** [8] found that 412 patients out of 1203 patients with COPD were still smokers (34%) and 770 patients were ex-smokers (64%). This confirms that the smoking habit increased the chance of developing COPD. 15% of active smokers developed COPD was reported by ***Sitkauskiene et al.*** [6] in Gutenberg, Sweden. They added that there are other risk factors including indoor air pollution (e.g. solid and fuel used for cooking and heating), outdoor air pollution and occupational exposure to dust and chemicals (vapors, irritants and fumes) [10]. Although, some patients in the current study (7 patients = 23.3%) showed increase of FEV_1 pred.% more than 12% or more than 200 ml but with no significant difference between pre and post BDT for all patients at the onset of the study as criteria of ***GOLD*** [2]. ***Bolton et al.*** [11] found that there were 25 patients (29.4%) out of 86 COPD patients in a cross section study in South Wales, U.K., had bronchoreversibility. The same incidence of bronchoreversibility ,like in our study, was reported by ***Agusti et al.*** [12] where 24% of clinically diagnosed 2164 patients in Barcelona University, Spain. In retrospective study, ***Marin et al.*** [8] in Zaragoza, Spain, showed that they found 332 patients (27.6%) out of 1203 patients with COPD without significant comorbidities had bronchoreversibility. All patients in this study were suffering from hypoxemia (mean PaO_2 = 63 mmHg) and 27 patients out of 30 patients were suffering from hypercapnia ($PaCO_2$ = 52.1 mmHg) at the onset of the study. Nearly the same results were reported by ***Chaouat et al.*** [13] in a study of 64 patients with COPD had mean PaO_2 of 63 mmHg and mean $PaCO_2$ was 49.8 mmHg. The mean pH in the current study was 7.346. It was shifted to the acidotic side before treatment. The mean pH of patients studied by ***Carrillo et al.*** [14] in Madrid, Spain, was 7.22. The mean FEV_1% was 29%; the severity of COPD was the cause of the difference of pH between both studies. In the present study, the mean CAT score of the patients at the onset of this study was 30.5, which was very high and indicated bad outcomes. ***Lari et al.*** [15] in a study of 82 stable COPD cases lived in Mashhad, Iran, with mean age 47 years old, found that the mean CAT score was 26.3. The better mean score of their study might be due to younger mean ages of their patients. ***Dodd et al.*** [16] reported that the mean CAT score in 261 patients with COPD in London, U.K., was 20.5. The large number of ***Dodd et al.*** [16] study and the different programs might be the cause of the decrease of CAT score than the patients of the present study. In this study, two weeks intervals of follow up for every patient were carried out for a period of 8 weeks. Six weeks of follow up to detect the response of inhaled and oral steroids added to bronchodilators in patients with stable COPD that was stated by ***Hantera and Abdel-Hafiz*** [17]. Follow up weakly for four weeks was decided by ***Littner et al.*** [18]. One month was designed for follow up of post exacerbation of COPD patients was reported by ***Matkovic et al.*** [19]**.** In the current study, with regular course of previous mentioned lines of treatment, significant improvement in the mean FEV_1% and FEV_1 / FVC pred. % had been occurred after 4 weeks and after 6 weeks where all means of PFT showed significant improvement. Highly significant improvement in all means of PFT occurred after 8 weeks. Two weeks after initiation of treatment of 41 patients with COPD, they showed significant improved mean of FEV_1% (1.4 to 1.9 liters), lasting until the end of the study (which was 6weeks) was reported by ***Weiner et al.*** [20]. Analyzing the individual response of FEV_1% in ***Weiner et al.*** [20] showed that 29 patients out of 41 patients (71%) had significant improvement (increase more than 20%) and 12 patients (29%) showed additional increase but not significant. In comparison with changes of FEV_1% in the present study on response to treatment and that of ***Weiner et al.*** [20], it showed nearly the same results. After 29 days of double blinded treatment trial of 169 patients with COPD (visits were made weekly), ***Littner et al.*** [18] found that FEV_1% increased after one week of treatment from mean FEV_1% was 1.08 liters (41% of predicted) to 1.2 liters (49%). In the present study, there was significant improvement of mean PaO_2 occurred after 4 weeks while mean $PaCO_2$ and mean pH showed significant improvement after 6 weeks. After 8 weeks, ABG parameters showed highly significant improvement. The mean pH in the current study showed significant improvement from

acidic edge 7.35 to normal pH after 6 weeks of treatment to 7.37 and remained normal until the end of the study. The mean CAT score of patients in the present study, showed highly significant decrease from 30.5 to 20 at the end of the 8 weeks of the treatment that indicated marked improvement. Individual analysis of CAT score showed that there were 13 patients (43%) had very high score, 17 patients (57%) had high score and no patients had moderate or low score before the treatment. After 8 weeks of treatment, no patients had very high score, only 11 patients (36.6%) had high score, 14 patients (46.7%) had moderate score and 5 patients (16.7%) had low score. ***Dodd et al.*** [(16)] reported that the mean CAT score decreased 2.9 points (from 20.5 to 17.6) of 261 patients with COPD (mean age was 69 years and mean FEV_1% was 51.1% of the predicted) after 8 weeks of medical therapy and pulmonary rehabilitation. Individual analysis showed that 162 patients had 3.8 points decrease, 88 had little decrease 1.1 points, 8 patients reported no difference and 3 patients reported feeling little worse. Big number of ***Dodd et al.*** [(16)] study might be the cause of apparent difference between their CAT score and that of the present study before treatment. Prospective study of 565 patients with COPD, (mean age was 70 years and mean FEV_1% was 47.6 % of the predicted) in Hospital and Pulmonary Clinics in England, Europe, for 8 weeks of treatment, ***Kon et al.*** [(21)] observed that mean CAT score decreased 3 points from 21.8 to 18.8. The results of the current study suggest that patients who were non-reversible according to BDT may still exhibit improvement of lung volumes following regular receiving of bronchodilators. Therefore, patient responses may vary over time between patients and within same patient from day to day or weeks. Classification of COPD by FEV_1% inadequate reporting disease severity. CAT score covers a broad range of effect of COPD on patient's health, despite the small number of component items. The CAT score should be improving communication between clinician and patient and give adequate assessment of severity of the disease and benefits of treatment. Finally, the present study provided evidence that patients with COPD who received adequate and continuous treatment became stabilized for a period of time without progressive decline of PFT, ABG or CAT. This would be good news for these patients.

CONCLUSION

Bronchoreversibility is not determined from the first session of nebulizer. Moreover, mostly there was no difference in pulmonary functions mainly FEV_1 between pre and post bronchodilator inhalation. To judge if there is airflow reversibility or not, we must give the patient complete course of treatment for at least one month. Therefore, the lack of acute response to SABA does not preclude the beneficial long-term bronchodilator treatment response. COPD is not curable but treatable disease. Therefore, the main goals of treatment are to improve pulmonary functions, decrease symptoms and decrease rate of exacerbations. Most of COPD patients have high to moderate clinical improvement, which is revealed by pulmonary functions, PaO_2 & $PaCO_2$ with complete course of treatment that consists of bronchodilators and ICS. Thus, the pharmacological lung reduction therapy through bronchodilators and ICS treatment have both important and obtainable goal in those patients. Most of COPD patients have good CAT score, which reveals the outcomes with complete course of treatment. CATest is the simplest, evaluating and applicable questionnaire rather than others like (SGRQ). This study showed some important implications for the care of COPD patients. As the patients reported that they had bad days and fear of exacerbations, they also experienced good days. Although the present study did not manage to include more than 30 stable COPD patients. It had diversities in the materials as regard age, sex, occupation, special habits, PFT, ABG and CAT score that made it to become comparable to other studies with high numbers of the patients. The combination of quality of life measures with the functional measures obtained from the spirometry may provide information and comprehensive evaluation of patients with COPD.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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