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Evaluation of the clinical use of nebulization therapy and antibiotics in in-patients with chronic obstructive pulmonary disease: A randomized prospective study at a tertiary care teaching hospital

Asfia Fatima[1*], Falak Naaz[1], Amatul Ali Sameera[1], Najiya Fatima[1], Mohd Mohiuddin Shareef[1], Musa Khan[2], Javed Akhtar Ansari[1].

[1]*Department of Pharmacy Practice (PharmD), MESCO College of Pharmacy, Mustaidpura, Hyderabad, India.*
[2]*Department of General Medicine, Osmania General Hospital (OGH), Afzal Gunj, Hyderabad, India.*

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*Author for correspondence
E-mail: asfiyafatima06@gmail.com

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ABSTRACT

Background: An observational, prospective study was conducted at a tertiary care teaching hospital in Hyderabad, T.S., India. The aim of this study was to evaluate the clinical use of nebulization therapy and antibiotics in in-patients with chronic obstructive pulmonary disease.

Subject and Methods: A total of 115 patients from the In-patient Department of General Medicine in Osmania General Hospital, who were prescribed nebulizers and antibiotics and those who fulfilled the exclusion and inclusion criteria were selected for the study which was conducted for 6 months. Information significant to the study was collected from the case records and discussions conducted with the in-patients and bystanders during ward rounds. Daily follow-ups were conducted to assemble data in therapy, add-on therapy and clinical improvement.

Results: The mean age was 59 years and the standard deviation was 11 years. Of the population, 77% were smokers and 51% were alcoholics. The most commonly used Bronchodilator is Deriphylline with a percentage of 78.10% and Antibiotic Monocef with a percentage of 72%. The most commonly used formulation is Orals with a percentage of 44.80%. A population of 43.50% of patients resulted with A grade severity index which represents low risk and low symptoms. 85% of individuals responded positively after the nebulization therapy with Oxygen therapy provided to them, as their SpO_2 levels with O_2 therapy changed into the normal range. There was a significant difference between the SpO_2 with O_2 percentages and SpO_2 without O_2 percentages ($\alpha = 0.05$).

Conclusion: Nebulization therapy had more clinical improvement when compared to Inhalation therapy as the Nebulizers require less intensive training for COPD patients. Antibiotics added to the treatment decreased the frequency of exacerbations.

Keywords: Chronic Obstructive Pulmonary Disease, Nebulization, Antibiotics.

INTRODUCTION

COPD is a known leading cause of morbidity and mortality worldwide which results in social and economic burden which is increasing progressively. COPD is a disease characterized as 'airflow limitation that is not fully reversible' by, World Health Organization, Global Obstructive Lung Disease (Pauwels et al., 2001) and American Thoracic Society (Celli and Mac Nee, 2004). This airflow limitation is associated with a progressive abnormal inflammatory response to noxious particles. World Health Organization (WHO) states COPD as the fourth leading cause of death in the world, with approximately 2.75 million deaths per annum, or 4.8% of total deaths. COPD has been considered as one of the main leading cause of death in many countries as follow: 1. United States of America: COPD is the fourth leading cause of death in USA (Celli and MacNee, 2004). A cohort study was conducted in the USA, which showed 1,301 out of 5,542 adults died due to COPD (National Health and Nutrition Examination Survey, NHANES); 2. Europe: Mortality rates vary from country to country, 20 per

100,000 population in Greece, Sweden, Iceland and Norway, up to more than 80 per 100,000 population in Ukraine and in Romania; 3. France: The mortality rate is approximately 40 deaths per 100,000 population (Loddenkemper et al., 2003); 4. China: Increase in the consumption of cigarette smoking in China, has increased the rate of mortality due to COPD. Tobacco is responsible for 12% of deaths, with projections which show that this rate could reach 30% in 2030 (Niu et al., 1993). 5. India: Crude estimates suggest there are 30 million COPD patients in India (Salvi and Agarwal, 2012). India contributes a significant and growing percentage of COPD mortality which is estimated to be amongst the highest in the world; i.e. more than 64.7 estimated age standardized death rate per 100,000 amongst both sexes. This would summarize to about 556,000 in case of India (>20%) out of a world total of 2,748,000 annually (Lopez et al., 2006). Mortality rate is higher in males than females and increases with age over 45 years old. The presence of COPD at various GOLD stages was associated with the following risk of death, as defined by hazard ratio (HR) (Liu et al., 2007). In addition to smoking, the other co-morbidities which are frequently associated with COPD is also important to consider such as, cardiovascular disorders, bronchial cancer, lung infections, thromboembolic disorders (Loddenkemper et al., 2003), asthma, high blood pressure, osteoporosis, joint pain, gastroduodenal ulcer, depression and anxiety (Sin et al., 2006). Active smoking is the main risk factor for COPD. The risk attributable to active smoking in COPD is thought to vary from 40% to 70%. In developing countries, exposure to pollution inside the home is an important risk for COPD. In particular for females, the smoke produced during cooking or method of heating in ventilated housing leads to an increase in pollution thus causing an increase in the risk of COPD. From an epidemiological point of view, males were classically more at risk of developing COPD in comparison with females because of their smoking habits. Depending on the country, females who smoke as much as males seem to have an equivalent risk of developing COPD (Liu et al., 2007; Mannino and Buist, 2007). Other than habitual reasons, infections play an important role in the occurrence of COPD, depending on age. During childhood, exposure to infections could alter the respiratory function of a child (Prescott et al., 1997). As an adult, the repeated occurrence of exacerbations which are viral or bacterial in origin could also contribute to lung function decline (Barker et al., 1991). The exposure to biomass fuels like crop residues or woods or animal dung is widely prevalent in India. The biomass effluent is released in the indoor living area where a significant proportion of this activity takes place and which constitutes more than one-half of the world's households. Biomass fuels are now considered a major cause of the causation of COPD and could be the single most common cause of COPD in the world. (de Koning and Smith, 1985; Salvi and Barnes, 2010). Ninety percent of rural households and 32% of urban households cook their meals on a biomass stove with only 25% of the cooking being done with cleaner gases (Salvi and Barnes, 2009). Management of severe exacerbation of COPD is based on relieving symptoms, as there is no curative therapy available. These strategies include $ß_2$ agonists, anticholinergics, corticosteroids which can be given i.v, antibiotic therapy when indicated, and the i.v. administration of methylxanthines such as aminophylline. Antibiotic therapy has been shown to have an important effect on clinical recovery and outcome in patients with acute exacerbations of chronic bronchitis and emphysema (Fein and Fein, 2000). Chronic Bronchitis is clinically defined as a chronic cough for at least three months for two consecutive years (Koda-Kimble, 2013). Initial therapy should focus on maintaining oxygen saturation at 90 percent or higher. Therefore, antibiotic administration should be considered at the beginning of treatment for exacerbations of COPD (Voelkel and Tuder, 2000). Other than pharmacological drugs, COPD can be treated by monitoring of oxygen status. Oxygen supplementation via external devices or mechanical ventilation may be indicated to maintain oxygen delivery to vital tissues. (Voelkel and Tuder, 2000). In severe exacerbations, a positive – pressure mask ventilation method (Eg: continuous positive airway pressure) and intubation are necessary to provide adequate oxygenation. Such interventions are more likely to be needed when hypercapnia is present, exacerbations are frequent or altered mental status is evident (Voelkel and Tuder, 2000). Nebuliser therapy is frequently prescribed for management of chronic obstructive pulmonary disease (COPD) (Saint et al., 1995; O'Driscoll, 1991). About half of the patients who remain breathless despite high-dose bronchodilators delivered by pressurized metered dose inhalers (pMDIs) or dry powder inhalers (DPIs), derive benefits from nebuliser therapy (Jarvis and Shiner, 2007).

The present study was carried out to evaluate the clinical use of nebulization therapy and antibiotics in in-patients with COPD.

SUBJECT AND METHODS

All the nebulizers and antibiotics containing prescription were monitored to know the frequency extent of nebulizer and antibiotic use and also the conditions in which it was prescribed. Rationality of prescriptions was evaluated by using the WHO core drug prescribing indicators, that is, (a) average number of drugs per encounter, (b) percentage of encounters with an antibiotic, (c) percentage of encounters with an injection, (d) percentage of drugs prescribed from the essential drugs list or formulary, (e) percentage of drugs prescribed by generic names. A standard data entry format was designed to collect patient's detail with reference to the nebulizers and antibiotics prescribed.

Study design

A hospital based prospective, observational study was carried out on 115 in-patients in Department of General Medicine, Osmania General Hospital, Hyderabad, T.S., India. The data was collected which contains patient demographics (age, sex), date of admission, date of discharge, history of present illness, past medical history, diagnosis, name of the drugs, dosage regimen (form, dose, route, frequency and duration). The knowledge assessment questionnaire form contains about 25 questions to assess the knowledge of patient towards the medications used.

A total of 115 patients from the in-patient department of general medicine in Osmania General Hospital, who were prescribed nebulizers and antibiotics and those who fulfilled the exclusion and inclusion criteria were selected for the study. The study was carried out for a period of six months.

In this study, patient's aged between 30 – 80 years of either sex, COPD with or without co-morbidities; smoking and alcoholic status was included.

The Out-patients, pregnant and patients on herbal medicines were excluded. Patient Demographic details (age, sex, alcoholic status, smoking status), Chief complaints, History of present illness, Past medical and medication history, Family history final diagnosis, name of the drug, dosage regimen (form, dose, route, frequency and duration), Date on which pharmacotherapy was initiated and laboratory data.

A suitable data collection form was designed and used with respect to : a) Demographic details: name, age, sex b) Condition and reasons for hospital admission were recorded and c) Drug data: brand and generic name of the drugs prescribed, dose, route of administration, frequency and their follow up for few days was recorded.

Statistical analysis

Statistical analysis was conducted by using ANOVA followed by *t*-test, paired *t*-test. SPSS Software 17.0 and Graph Pad Prism 6 were used.

RESULTS

According to the plan of work, Rationality of prescriptions was evaluated by using the WHO core drug prescribing indicators, which resulted as: (a) Average number of drugs per encounter: 10 drugs; (b) Percentage of encounters with an antibiotic: 37%; (c) Percentage of encounters with an injection: 41.5% (d) Percentage of drugs prescribed from the essential drugs list or formulary: 60% (e) Percentage of drugs prescribed by generic names: 18.1%.

Population description: A total of 115 patients with presumed/confirmed COPD. The Mean Age was 59 years and the standard deviation was 11 years. Of the population, 88.5% were males and 11.5% were females, 77% were smokers and 23% were non-smokers. The main demographic and clinical characteristics, co-morbidities have been described later.

Table 1. Distribution of subjects based upon age (%).

Age Group (In years)	Percentages
31-40	11.81%
41-50	12.20%
51-60	24.43%
61-70	42.36%
71-80	8.13%

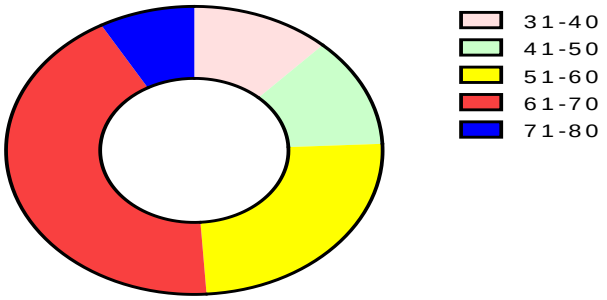

Figure 1. Distribution of subjects based upon age (%).

Among the study population, 48 individuals belonged to the age group of 61-70 years, 29 individuals belonged to the age group of 51-60 years, 14 individuals belonged to the age group of 31-40 years, 13 individuals belonged to the age group of 41-50 years and 11 individuals belonged to the age group of 71-80 years.

Table 2. Distribution of subjects based upon gender (%)

Gender	Percentages
Male	88.50%
Female	11.50%

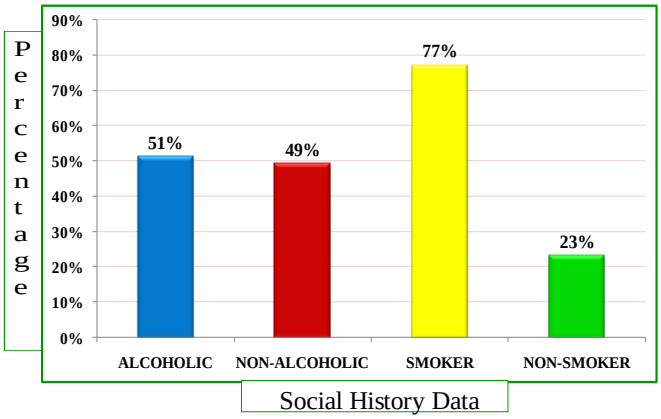

Figure 2. Distribution of subjects based upon social history (%).

Among the study population, 57 individuals were alcoholics and 87 of individuals were smokers and a total of 22 individuals were neither alcoholics nor smokers.

Culture sensitivity test: In the present study, of the 115 patients, 80 were advised for culture sensitivity test. No Pathogenic Organism was found.

Table 3. Percentage of drugs used.

Formulations	Name of Drugs	Percentages
Injection	Deriphylline	78.1
Injection	Hydrocortisone	49.75
Nebulizer	Asthalin	71.5
Nebulizer	Budecort	57.5
Injection	Azithromycin	48.65
Injection	Monocef	72
Nebulizer	Duolin	23.8
Injection	Piptaz	5.4
Capsule	Amoxicillin	15.7
Tablet	Cifran	4.5
Tablet	Levofloxacin	3.85

Among the study population, the most commonly used Bronchodilator is Deriphylline with a percentage of 78.10% and the most commonly used Antibiotic is Monocef with a percentage of 72%.

Table 4. Percentage of formulations used.

Formulations	Percentages
Nebulizers	23.20%
Injections	30%
Inhalers	2%
Orals	44.80%

Among the study population, the most commonly used formulation is Orals with a percentage of 44.80% followed by Injections with a percentage of 30%, Nebulizers with a percentage of 23.20% and the least common is Inhalers with a percentage of 2%.

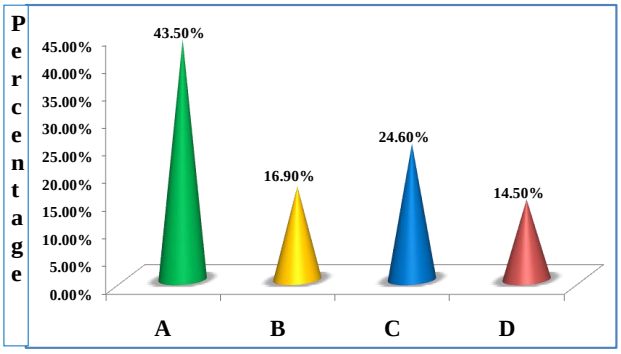

Figure 3. Results of COPD severity assessment.

Among the study population, 43.50% of patients resulted with A grade severity index which represents Low risk and Low symptoms, 24.60% of patients resulted with C grade severity index which represents High Risk and Less Symptoms, 16.90% of patients resulted with B grade severity index which represented Low Risk and More Symptoms and 14.50% of patients resulted with D grade severity index which represented High Risk and High Symptoms.

Table 5. Results of the type of disease.

Types of Diseases	Percentages
COPD with comorbidities	58.45%
COPD without comorbidities	41.45%

Among the study population, 67 individuals suffering from COPD with comorbodities resulted in a percentage of 58.45% and 48 individuals suffering from COPD without comorbidities resulted in a percentage of 41.45%.

Table 6. Changes in O_2 saturation before and after nebulization therapy.

No of Patients	SpO_2 with O_2	SpO_2 without O_2
1-5	99	60
6-10	98	66
11-15	86	50
16-20	96	87
21-25	92	70
26-30	95	89
31-35	95	90
36-40	98	75
41-45	97	70
46-50	98	70
51-55	90	60
56-60	99	77
61-65	96	86
66-70	92	89
71-75	96	60
76-80	89	80
81-85	95	90
86-90	95	76
91-95	99	89
96-100	98	60
101-105	96	80
106-110	92	65
111-115	80	70

Statistical Presentation of the Data

Statistical presentation of SpO_2 with O_2 data

Table 7. One-sample statistics.

	N	Mean	Std. Deviation	Std. Error Mean
SpO_2 With O_2	115	75.22	34.304	3.213

Table 8. One-Sample Test

	Test Value = 0					
	T	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
SpO_2 With O_2	23.412	114	.005	75.219	68.85	81.58

Statistical presentation of SpO_2 without O_2 data

Table 9. One-Sample Statistics

	N	Mean	Std. Deviation	Std. Error Mean
SpO_2 Without O_2	115	65.72	31.687	2.968

Table 10. One-Sample Test

	Test Value = 0					
	t	df	Sig. (2 tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
SpO_2 Without O_2	22.144	114	.005	65.719	59.84	71.60

Among the study population, 98 individuals had effect on SpO_2 levels whereas 17 individuals had no effect on SpO_2 levels.85% of individuals responded in a positive way after the nebulization therapy provided to them , as their SpO_2 levels with O_2 therapy changed into the normal range i.e. 86.1± 7.7.

DISCUSSION

The rationality of prescription was evaluated by using the WHO core drug prescribing indicators which was developed and published by WHO and INRUD (Lange et al., 1990). It resulted as the average number of drugs per encounter was found to be 10 drugs, Percentage of encounters with an antibiotic was 37%, Percentage of encounters with an injection was 41.5%, Percentage of drugs prescribed from the essential drug list was 60% and the Percentage of drugs prescribed by generic names was 18.1%. Thus, it was found to be irrational use of the drugs as two drugs per encounter is the rational use of drugs as per the previous studies.

The age groups between 30-80 years were admitted during the period of study. The age groups between 30-40 years were found to be 11.81% whereas in study conducted previously only above 40 years of age were admitted during their period of study (Sajesh et al., 2014). The majority of patients were between 61-70 years of age group (42.36%). There is a significant difference between the different age groups (α = 0.05).

The sex wise distribution added support to the evidence of the previous studies that majority of the patients were of male sex, which was as high as 88.50%. The females accounted for around 11.50%. Male to Female ratio observed in our study is 8:1. This only confirmed the finding of the previous study conducted that males accounted for the majority of the disease burden.

The alcoholic status distribution resulted that majority of the patients were alcoholic which was as high as 51%. The non-alcoholics accounted for around 49%. There is not much significant difference between alcoholics and non-alcoholics.

Active smoking is the main risk factor for COPD. The risk attributable to active smoking in COPD is thought to vary from 40% to 70% according to the country (Boutin-Forzano S, 2007). The smoking status distribution added to the evidence of the previous study that the impact of smoking is directly related to the worsening of the COPD (Zhukova , Konyshkina, Kononova, 2015). In present study, the smokers accounted for around 77% and non-smokers accounted for 23% making smoking as a potential risk hazard for COPD patients.

In present study, the Culture Sensitivity Test was performed in COPD patients who resulted in no pathogenic organism growth.

The use of methylxanthines was minimal in other study inspite of they were one of the most freely available drugs in the hospital in which the study was under taken. The percentage of drugs used were calculated which resulted as the most commonly used bronchodilator to be Deriphylline accounting of about 78.10%. Antibiotics were used in 86.7% patients which may be an indicator of the prevalence of infections among the patients admitted with acute exacerbation of COPD in different demographic areas. (Sajesh et al., 2014) The most commonly used antibiotic to be Monocef accounting of about 72%.

Corticosteroids remain a standard of care for AECOPD secondary to their documented efficacy in improving airflow and gas exchange (increasing FEV_1 and PaO_2), as well as improving dyspnea, hastening recovery, and reducing length of hospitalization and rate of relapse at 30 days. In the previous study, the Systemic corticosteroid is efficacious in the treatment of AECOPD and is considered as the standard care for COPD patients. In the present study, the systemic corticosteroids accounted for only about 49.75% which included the Intravenous Injection of Hydrocortisone. Therefore in our study, the use of systemic corticosteroid is used as an additional therapy to treat COPD along with different medications.

In the present study, azithromycin was found to decrease the frequency of exacerbations and reoccurrence of incidence of COPD, which accounted for

about 48.65% ,but was not given to all the COPD patients as it lead to some serious ill effects. It supported the study conducted by Richard K et al who concluded that among selected subjects with COPD, azithromycin was taken daily for 1 year, when added to usual treatment, decreased the frequency of exacerbations and improved quality of life but caused hearing decrements in a small percentage of subjects. Although this intervention could change microbial resistance patterns, the effect of this change was not known (Albert et al., 2011).

The oral formulation accounted the highest percentage used during the study which was around 44.80%, followed by the injections which were around 30%, nebulizers which was around 23.20% and the least percentage used was inhalers which were around 2%.

The uses of Nebulization therapy are preferred over Inhalation therapy as the formulation of Nebulizers account around 23.20% and the inhalers account around 2%. Despite several known drawbacks associated with nebulized therapy, it is recommended that maintenance therapy with nebulizers should be employed in elderly patients, those with severe disease and frequent exacerbations, and those with physical and/or cognitive limitations (Dhand, 2012) as it is easy to use and results in a positive manner than inhalation therapy.

The CAT and the mMRC are validated tools that assess symptoms which are further assessed by COPD staging Assessment tool. In the previous studies, different studies assessed different stages of severity in COPD. In the present study, the majority of the patients were assessed as Grade A in the severity staging assessment tool. Grade A indicates low risk, low symptoms includes patients with low level of symptoms as judged by a COPD Assessment Test (CAT) score <10, or a modified Medical Research Council Dyspnea Scale (mMRC) score <2 and 0-1 exacerbations in the previous year.

Majority of the patients in the study had co-morbid conditions accounting of about 58.45% and patients without co-morbid conditions accounted for 41.45% which was similar as compared to the earlier studies conducted (Koda-Kimble, 1990). The most commonly observed co-morbid condition was alcoholism (51%). The other co-morbid conditions found were acute renal failure, diabetes mellitus, congestive cardiac failure, hypothyroidism. In the previous study, there was no significant change in the SpO_2 levels before and after the ODN was given (Hong et al., 2014). In the present study, there was a significant difference between the values of SpO_2 with O_2 and SpO_2 without O_2 (Significant Difference = 0.005). The levels of SpO_2 with the oxygenation were changed in the normal range after the Nebulization therapy was given.

CONCLUSION

In the present study, we performed a randomized, prospective and observational study on patient in Osmania General Hospital to evaluate the clinical use of nebulization and antibiotic therapy, in In-patients admitted to the hospital with a clinical diagnosis of COPD. The study was conducted in 115 patients to evaluate the efficacy of nebulization therapy in COPD patients. During the study, the SpO_2 levels were monitored and recorded as the parameter to evluate the efficacy of the Nebulization therapy. After the study, it was found that 85% of individuals showed a positive response to the nebulization therapy as their SpO_2 levels recovered in the normal ranges. Asthalin and Monocef was found to be most commonly used in COPD patients. During the study, Culture Sensitivity Test was performed to assess and diagnose the COPD. After the study, it was found that 80 patients who were advised for culture sensitivity test, were resulted in no Pathogenic Organism Growth. Severity of COPD was calculated based on the CAT and mMrc scores ,where patients resulted with an A grade Severity index i.e. Low Risk, Low Symptoms. Thus, from our study we have concluded that the Nebulisation therapy have more clinical improvemnet when compared to Inhalation therapy as the Nebulisers required less intensive training for COPD Patients. Antibiotics added to the treatment decreased the frequency of exacerbations. The patient should be educated about the rational use of the drug to decrease the risk of COPD.

CONFLICT OF INTEREST

None declared.

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