ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Use Of Sublingual Bacterial Lysates In Stable COPD: A Case Control Study.

Haadi Nizar Ahammed*, and Tushar Saharsabudhe.

Department of Respiratory Medicine, DR. D. Y. Patil Medical College Hospital & Research Centre, Pune, Maharashtra, India.

ABSTRACT

Bacterial infection due to colonizers is the commonest reason for exacerbation in COPD. A vaccination strategy of administering antigens extracted from a lysate of the most common bacterial species involved in respiratory exacerbation may thus reduce exacerbation rate. To evaluate the safety and efficacy of sublingual bacterial lysates in reducing COPD exacerbation and control of COPD. In this open labelled case-control study, 100 patients of COPD were randomized into two different groups after being matched for severity and age. The treatment group received a daily sublingual dose of bacterial lysate (10 days each month for three consecutive months) and the control group did not. Patients were followed up with 7 visits over 1 year to evaluate COPD control. Treatment group showed statistically significant reduction in decline of FEV1 and improvement in QOL, CAT score and BODE index over 1 year. There were 21 major exacerbations in control group vs. 12 in the treatment group. Bacterial lysate had no adverse effects. Immunization with bacterial lysates showed improvement in QOL, number of major COPD exacerbations and slowed down the disease progression.

Keywords: COPD , Sub lingual Bacterial Lysates ,CAT score , BODE index,FEV1.

https://doi.org/10.33887/rjpbcs/2021.12.1.12

Corresponding author

ISSN: 0975-8585

INTRODUCTION

GOLD defines COPD as a common , preventable and treatable disease that is characterised 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 and influenced by host factors including abnormal lung development[1] .It is a major cause of morbidity and mortality worldwide and is among the top 10 global contributors to global burden of disease as measured by disability adjusted in life years[2]. According to world health organisation (WHO), the total number of deaths worldwide from COPD are projected to increase beyond 30% in the next 10 years and by 2030, COPD would become the fourth leading cause of death worldwide[3]. Approximately 14 million Indians currently suffer from COPD. In India it i s more common in males compared to females, the ratio being 5:2.7[4].

Patients with chronic obstructive pulmonary disease (COPD) are prone to exacerbations, which account for significant morbidity and mortality and are a key determinant of health-related quality of life. (Seemungal et al 1998)[5]. COPD exacerbations are defined as a change in the patient's chronic respiratory symptoms sufficient to warrant a change in management (Celli et al 2004; Global Initiative for Chronic Obstructive Lung Disease 2005)[6].

The lower airways of 25% to 50% of COPD patients are colonized by bacteria, especially noncapsulated Haemophilus influenzae, Streptococcus pneumoniae, and Moraxella catarrhalis (Anthonisen et al 1987; Cabello 1997)[7,8]. The predominant bacteria recovered in the lower airways of patients with mild exacerbations are H. influenzae, S. pneumoniae and M. catarrhalis, whereas in severe COPD requiring mechanical ventilation gram negative bacilli, and P. aeruginosa are more frequent (Papi et al 2006)[9]. Lower airway bacterial colonization is increasingly recognized as an independent stimulus to airway inflammation (Sethi et al 2001)[10] It can modulate the character and frequency of COPD exacerbations (Patel et al 2002)[11].

Bacterial lysates have been developed as vaccines since 1983 as one of the preventive measures for exacerbations in COPD[12]. The Polyvalent Mechanical Bacterial Lysate (PMBL), is useful against several bacteria that are responsible for infections in respiratory tract. It is both specific and non- specific immunomodulator. It is a freeze dried bacterial lysate formed by mechanical lysis of following organisms[13] Streptococcus pneumoniae, Haemophilus influenza, Moraxella catarrhalis, Staphylococcus aureus, Streptococcus pyogenes, Streptococcus viridans, Klebsiella pneumonia, Klebsiella ozaenae. Inactivated micro-organisms offer certain advantages as a potential vaccine for mucosal immunization [Cazzola et al. 2008][14]. They are naturally occurring micro particles, which possess multiple antigens and are relatively inexpensive to produce. These immunomodulatory bacterial extracts are commonly administered by the oral route.

There is no enough published data on safety and efficacy of PMBL more especially Indian population although it has been marketed and used by physicians all over India. Hence the present study was intended to generate data on Indian population.

MATERIALS AND METHODS

This was a CASE CONTROL STUDY which included randomly selected adult male and female patients above the age of 40 years in two groups of 50 each, diagnosed as COPD based on GOLD criteria and willing to give written and informed consent who had attended the Out Patient Department (OPD) of at Department of Respiratory Medicine, Dr. D.Y. Patil Medical College, Hospital and Research Centre, Pimpri, Pune between September 2018 and August 2020. Patients who were immunocompromised, who had exacerbations in past 4 weeks (defined by GOLD) and with ongoing smoking habits were excluded from the study. The patients who had withdrawn the consent, those with poor compliance or got relocated and was lost to follow up were removed from the study.

Patients were confirmed as COPD based on GOLD GUIDELINES. Spirometry was performed on all patients using an electronic spirometer (COSMED Pulmonary Function equipment – Model Quark PFT 2008) to confirm the diagnosis of COPD.

7 study visits were planned with scheduled events and protocol.

ISSN: 0975-8585

The VISIT 1(DAY X-14) was meant for Enrollment .Confirmed cases of COPD using GOLD criteria, using inclusion and exclusion criteria, suitable subjects were enrolled down. All those enrolled had their PFT and X ray done. VISIT 2 was Randomization visit (DAY X) were subjects, using randomization were either categorized as a case or a control. They had their general examination and basic routine done prior to the administration of test drug irrespective of case and control. The functional status and quality of life in COPD patients were assessed using CAT score /BODE index prior to test drug was administrated. The drug then was given to the patient during that visit and was called upon after 15 days. In VISIT 3; 4 and 5 with a gap of 1 month, the safety and efficacy of drug in COPD patient was assessed through PFT/CAT SCORE/BODE INDEX. General examination and routine investigation was done. VISIT 6 and 7 had same protocol of previous visit with time gap of 3 months.

RESULTS

In this study all 100 patients were above 40 years old. In cases the maximum number of patients were seen in age group of 51to 60 which was 28 % of cases and in controls it was in age group of 71 to 80 which was 34%. 62% belonged to male gender and 38% belonged to female gender in cases and controls respectively. The male to female ratio diagnosed with COPD in this was 1.9:1.18 in each study group. (TABLE 1)

Table 1: Baseline Characteristics of Study Participants

VARIABLES	FREQUENCY		PERCENTAGE	
AGE	CASES	CONTROLS	CASES (50)	CONTROLS(50)
40-50	9	5	18%	10%
51-60	14	14	28%	28%
61-70	11	12	22%	24%
71-80	13	17	26%	34%
81-90	3	2	6%	4%
GENDER				
MALE	31	31	62%	62%
FEMALE	19	19	38%	38%
GOLD STAGE				
1	0	1	0	2%
2	24	23	48	46%
3	23	24	46	48%
4	3	2	6	4%

VARIABLES	VISIT 1 (before treatment)	
	CASES	CONTROLS
FEV1	49.04(12.92)*	50.76(15.9)*
BODE INDEX	4.54(1.35)*	4.64(1.75)*
CAT SCORE	15.62(4.3)*	17.7(4.83)*
FEV1	49.04(12.92)*	50.76(15.9)*

*Values with Standard Deviation

Maximum number of patients got accommodated into GOLD stage 2 and stage 3 in both cases and controls respectively. 48% of cases and 46% of controls belonged to GOLD stage 2. 46% of cases and 48% of controls belonged to GOLD stage 3. (TABLE1).

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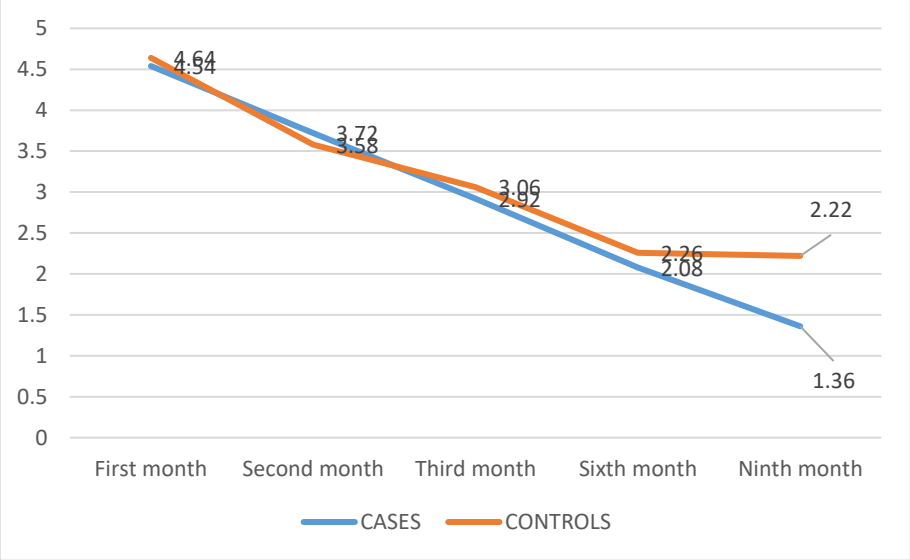
Table 2 and Graph 2 Showing distribution of the patients according to mean BODE INDEX month wise in both cases and controls

Bode scoring	Cases (50)	Controls (50)	T statistic	P value
First month	4.54±1.35	4.64±1.75	0.25	0.07
Second month	3.72±1.42	3.58±1.48	0.48	0.77
Third month	2.92±1.44	3.06±1.5	0.47	0.72
Sixth month	2.08±1.35	2.26±1.27	0.68	0.67
Ninth month	1.36±0.98	2.22±1.21	3.9	**0.01**

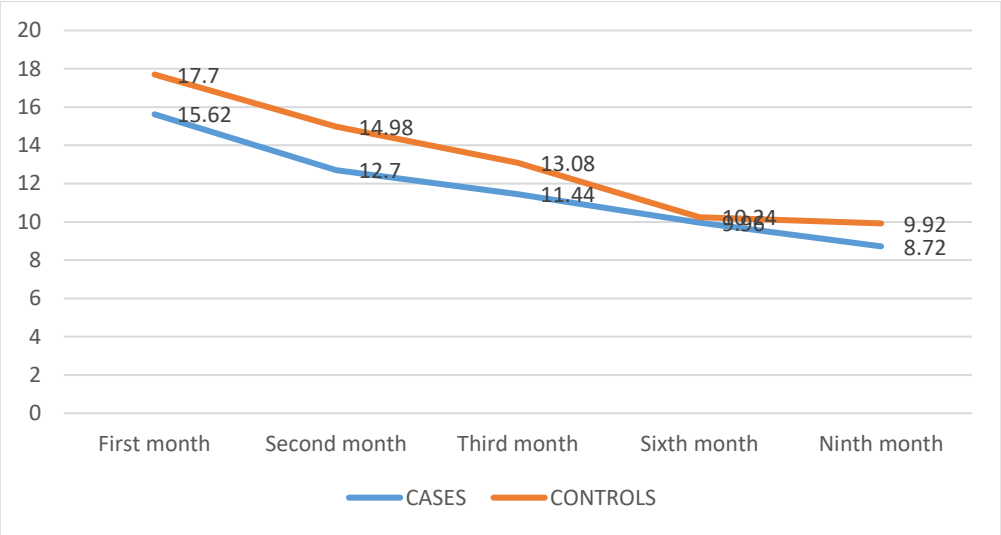


BODE INDEX shows significant improvement with cases who were given with BL to that of controls in the ninth month. The mean value of BODE INDEX in cases in the first month was 4.54±1.35 and that of controls was 4.64±1.75 with p value of 0.07. The mean value at last follow up month was1.36±0.98 in cases and that of control was 2.22±1.21 and p value obtained was 0.01.

Table3 and Graph 3 showing distribution of the patients according to mean CAT scoring month wise in both cases and controls

CAT scoring	Cases (50)	Controls (50)	T statistic	P value
First month	15.62±4.3	17.7±4.83	2.27	**0.025***
Second month	12.7±3.93	14.98±4.54	2.68	**<0.005***
Third month	11.44±3.7	13.08±4.94	7.01	**<0.001***
Sixth month	9.96±3.25	10.24±4.53	1.94	**0.02***
Ninth month	8.72±3.14	9.92±4.76	2.29	**0.004***

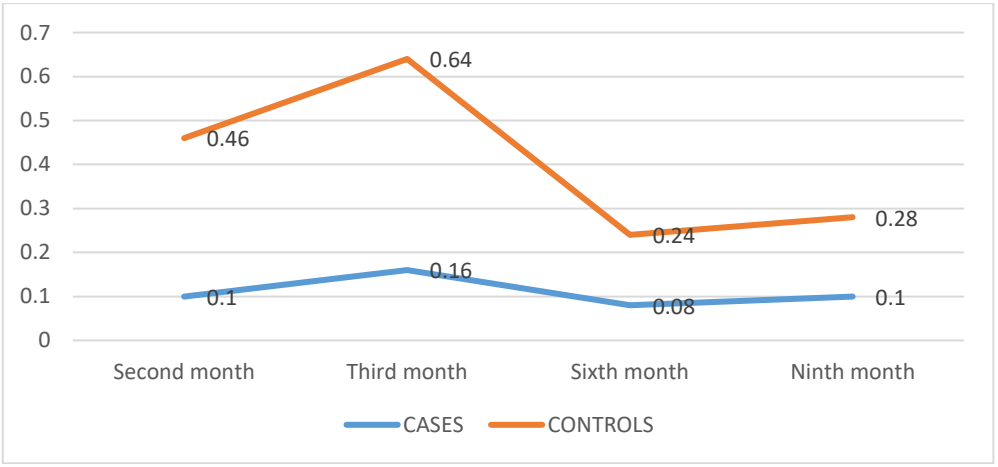
ISSN: 0975-8585



The mean CAT scoring during first month of visit in cases was 15.62±4.3 and that of controls was 17.7±4.83 (p value =0.025) and during the last visit was 8.72±3.14 and 9.92±4.76 (p value =0.004) respectively .CAT score has shown significant improvement throughout the visits in cases when compared to controls.

Table 4 and Graph 4 showing distribution of the patients according to decrement of FEV1 month wise in both cases and controls

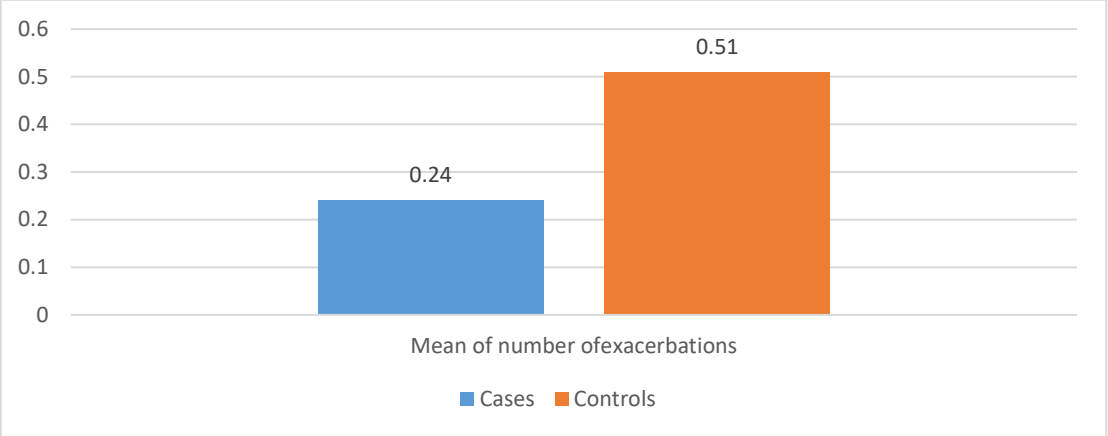
FEV1 decrement	Cases (50)	Controls (50)	T statistic	P value
Second month	0.10±0.41	0.46±1.26	2.007	**<0.001**
Third month	0.16±0.58	0.64±1.25	2.43	**<0.001**
Sixth month	0.08±0.39	0.24±0.84	1.26	**<0.001**
Ninth month	0.1±0.41	0.28±0.9	1.29	**<0.001**



The mean value of FeV1 decrement in controls in the third month and ninth month was 0.64±1.25 and 0.28±0.9 respectively in cases. In controls it was 0.16±0.580 and 0.1±0.41 third and ninth month respectively. Significant difference in FEV1decrement values was there when controls were compared to cases throughout all visits which was statistically proven. The mean values of FEV1 decrement was on higher side in controls than in cases due to increased number of exacerbations promoting the acceleration of disease process.

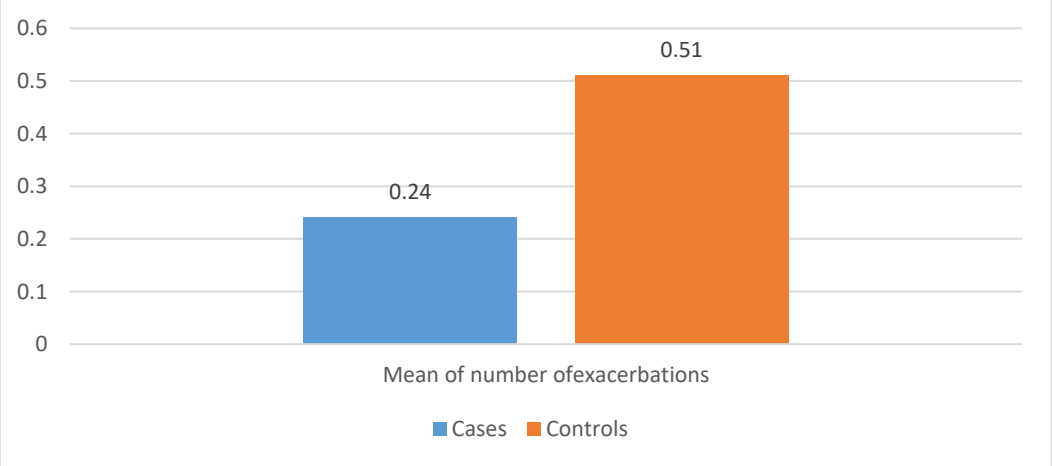
ISSN: 0975-8585

Graph 5 showing the distribution of the patients according to mean number of major exacerbations in both cases and controls



Through statistical analysis it was proven that there is significant episodes of exacerbation in controls than in cases. The mean number of major exacerbations in cases was 0.24±0.43 and control was 0.51±0.64 with p value of 0.020.

Graph 6 showing the distribution of the patients according to mean number of major exacerbations in both cases and controls



The statistical analysis have proven that there is significant expenditure for the sake of treatment including hospitalization in controls than in cases. The mean expenditure in cases and controls were 1567±147.63 and 1635±233.48 respectively with p value of 0.001

DISCUSSION

COPD is rated as one of the top 10 contributors to global burden of diseases [15] .By 2030, WHO estimates that COPD would rank fourth leading cause of death worldwide[16] ·AECOPD can be defined as worsening of respiratory symptoms beyond normal day to day variations leading to change in medication [17].The most common cause of an exacerbation in COPD is viral or bacterial infections [18].

In COPD patients, 25% to 50% of them will have their lower airways colonized with bacteria, especially noncapsulated Haemophilus influenzae, Streptococcus pneumoniae, and Moraxella catarrhalis (Anthonisen et al 1987[7]; Cabello 1997[8]). In case of mild exacerbations the bacteria isolated were H. influenzae, S. pneumoniae and M. catarrhalis, while in severe COPD gram negative bacilli, and P. aeruginosa are the main culprit (Papi et al 2006[19]). One of the independent factor much recognized that act as stimulus in Lower airway for airway

inflammation is bacterial colonization (Sethi et al 2010[20]) It can modulate the character and frequency of COPD exacerbations (Patel et al 2002)[11]. Influenza and Pneumococcal vaccines have shown to reduce the frequency of exacerbations and hospitalizations in COPD[21].

Recently, a new technique based on mechanical lysis has helped to evolve a new type of bacterial lysate which has been approved for vaccination. The Bacterial Lysate (BL) which has already been approved for the use of vaccination, is being used here, which is a killed, freeze-dried bacterial lysate obtained by mechanical lysis of the eight respiratory pathogens).

BL tablets are administered sublingually for easy distribution of the antigens in the upper respiratory tract mucous membrane and stimulate regional immunity. BL tablets are administered sublingually repeatedly for 10 days a month for 3 consecutive months.

The case control study undertaken by us, were to an extent was able to answer the question put forward by Soler (2005) [22], in spite that by considering the mechanism of action of BL is different to that of inhaled 'standard treatments' for COPD (inhaled anti-inflammatory and/or bronchodilator regimen) when combined had an addictive effect providing protection from COPD exacerbations.

The platform for the selected case control study was a tertiary hospital based in Pune, where randomization was the technique used for reducing the difference among groups so as to prevent unintentional errors and bias. The site for study was Department of Respiratory Medicine OPD. With strict adherence to the inclusion and exclusion criteria, a sample size consisting of 100 patients (50 each in case and control group) was organized. Aim of study being to assess the efficacy of use of sublingual bacterial lysates in stable COPD.

In the study, 62% of cases as well as in controls belonged to male gender and rest 38 % were of females. Here the male to female ratio in cases and controls was 1.9:1.18 and in Indian population median ratio is 1.6:1[23]. The prevalence of COPD in India in rural ranges in between 6.5% and 7.7% and 9.9% in urban areas as per systemic review from major studies [23] .

CAT scoring which is to assess the functional status of COPD patients, was used in the study, that had shown greater statistical significance of difference between cases and controls proving there was improvement in symptoms following each visits after initiation of the BL. The mean CAT score on the first month (i.e. after a month of first course of 10 tablets) in cases was 15.62±4.3 when compared to controls which was 17.7±4.83 pointing to significant improvement (p value=0.025*). The mean CAT SCORE of cases in first visit was15.62±4.3 which improved to 8.72±3.14 at the last visit. The CAT score is of eight items (cough, phlegm, chest tightness, breathlessness, limited activities, confidence leaving home, sleeplessness and energy) defined with contrasting adjectives. Most of the factors were found to be influenced by immunization. Thus improving the QOL. The study by Li J et al also supports our study which shows CAT score improvement seen with BL in cases even though he used improvement in respiratory symptoms put forward by patients as a scale to measure.

A double blinded placebo controlled randomised clinical trial with 381 patients was done. It was done to evaluate the efficacy of immunostimulating agent OM-85BV to prevent acute respiratory exacerbations in COPD patients. The trial resulted in 55% reduction in hospitalisation for respiratory problems and also the course of dyspnoea study in OM-85BV group was improved in contrast to placebo group[24].

In our study, significant difference in mean value of FEV1 decrement was seen in controls when compared to cases in each visits thus reflecting number of exacerbation the controls had contracted with worsening symptoms thus accelerating progression of the disease. The cases who had noticeable decrement in FEV1 might have had exacerbations from atypical organisms or viruses that might not have covered with oral BL vaccine. The mean value of FEV1 decrement in controls in the third month and ninth month was 0.64±1.25 and 0.28±0.9 respectively (the mean FEV1 decrement value of controls in each visit have always remained on higher side when compared to cases). In cases it was 0.16±0.58 and 0.1±0.41 in third and ninth month respectively after BL administration thus stating the number of exacerbations have come down in cases than in controls. This somehow proves that the BL may not have a direct effect on the underlying pathophysiology of the disease but may slow down the progression of disease by controlling the infection (bringing down the exacerbations). It has been shown that frequent exacerbations are associated with faster FeV1 decline[25]. So, early and effective treatment and prevention of exacerbation should reduce the rate of decline. In other study by Nadig et al. with

sample size of 24, observed that there was no change in lung function tests but, the FeV1 /FVC ratio showed a statistically significant improvement which was clinically insignificant. Li j et al with sample size of 90 patients under observation for 1 year which was case control study couldn't observe changes in airflow limitation but shown improvement in respiratory symptom scores compared to placebo. The authors in that study concluded that this was probably due to short course of treatment [26].

In this case control study in COPD patients with oral immunostimulant the response to vaccine was objectively measured using the BODE INDEX. It was during ninth month a statistical significant difference in the mean BODE index with improvement in cases than to control was made out. Improvement was due to reduction in the number of exacerbation and preventing further FEV1 decrement hence leading to improvement or preventing further reduction in exercise capacity and dyspnoea. The mean BODE INDEX in cases was 1.36±0.98 and controls was 2.22±1.21 in ninth month. As the months advanced with each follow up, as we have seen with CAT score, there was improvement in BODE INDEX within the cases. The component of BODE which mostly varied from its baseline was FeV1 for which it reflected the acceleration of the disease with each exacerbation. Henceforth the BL helped to slow down the disease progression by reducing the frequency of exacerbation though it doesn't play a direct role in pathogenesis of COPD rather have a beneficial add on effect.

FeV1 decrement, CAT score, BODE INDEX statistics throws light over and predicts the group of patients might have faced the maximum number of exacerbations and greater economic burden. The number of exacerbations were significantly more in controls than in cases with mean of 0.24±0.43 in cases and 0.51±0.64 in controls. In a study of F.Braido et al, sample size was almost comparable with us, 90 COPD patients were randomized as cases and controls. By the end of the one-year follow up, incidence, duration and severity of acute exacerbation shown significant decrease in the treated patients when compared to the placebo group ($p < 0.05$ in all cases). Solèr et al confirmed the efficacy of this BL agent in a slightly younger population with mild COPD or chronic bronchitis[22]. His study reported a significantly higher probability for patients treated with BL to remain free of acute exacerbations events ($p = 0.014$). It was found that the impact of BL was more significant among patients suffering from 2 or more acute exacerbation episodes ($p = 0.001$).

Similarly the economic burden was significantly more in controls than in cases with mean values of Rs.1635±233.48 and 1567±147.63 respectively. The preventive role of BL in reducing exacerbations in elderly patients with chronic bronchitis and COPD was confirmed in several clinical trials. In study conducted by Collet et al. ,191 elderly with chronic bronchitis and COPD reported a 55% decrease in the number of days of hospitalization and in the duration of stay in the control group than to placebo ($p = 0.037$) . When COPD taken to consideration, a reduction in the number of acute exacerbations, or a shorter duration of hospitalization, could represent an actual opportunity for cutting down of costs of management in patients. Patients with a moderate-severe COPD can experience a mean of at least 2 AECB/year (Miravitlles et al 1999). The most serious patients, besides experiencing more frequent exacerbations, are more frequently hospitalized, and for longer periods. The largest of all expenditures for patients with COPD is hospitalization related costs. The National Medical Expenditure Survey study estimated that per capita expenditures for inpatient hospitalizations in the COPD cohort were 2.7 times the per capita expenditures of the non-COPD cohort ($5,409 vs$2,001). Treatments that could prevent or limit hospitalizations could substantially impact the overall burden of this disease.

Limitations of this study

- Sample size of 100 patients was small because of time constraint, unwillingness to participate and repeated follow ups.
- Unable to study the mechanism of action such as evaluation of sputum macrophages and serum immunoglobulin as done in other studies which could have added more value to the study.

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