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ORIGINAL ARTICLE

Effect of Probiotic Oral Suspension on Disease Severity in Chronic Obstructive Pulmonary Disease Patients-A Randomized Control Trial

MUHAMMAD YOUNUS[1], KAMAL DIN[2], SOHAIL ANWAR[3], YASIR NASIR[2]
[1]Department of Pulmonology, Gujranwala Medical College
[2]Department of Pulmonology, King Edward Medical University
[3]Associate Professor, Department of Pulmonology, University College of Medicine & Dentistry, The University of Lahore
Correspondence to: Muhammad Younus, Email: dr.muhammadyounus79@gmail.com, Cell: 0331-4351365

ABSTRACT

Introduction: Probiotics has been broadly used in the healing of respiratory illness, but their efficacy for treating chronic obstructive pulmonary disease (COPD) has not been well studied.

Objective: To determine the effects of probiotic oral suspensions on disease severity in COPD patients assessed by Rate of exacerbation, COPD assessment Test (CAT) Score and C - reactive protein (CRP).

Material and Method: This Randomized controlled study was conducted at Institute of TB and Chest medicine (indoor and outdoor both), Mayo Hospital Lahore. Duration of study was one year, September 2020 to August 2021.Total 80 patients fulfilling the inclusion criteria are taken from the chest medical ward, Mayo Hospital Lahore. Their basic demographic information was recorded. Recruitment and randomization of patients was done. Cases were given Probiotic ampule (Enterogermina sachets containing Bacillus Clausii) 2 billion daily for 6 months and controls were given placebo. Patients were followed on monthly basis and they were assessed Rate of exacerbation, COPD assessment test (CAT) Score and CRP. Data was entered by SPSS-26. Quantitative variables like age was represented as mean + a SD. Qualitative variable like gender was represented as frequency and percentage. Comparison of two groups Placebo and probiotic group was carried out by independent sample t-test. p-value <0.05 taken as significant.

Results: Mean age of patients in treatment along with in placebo assembly was 48.27±11.67 and 49.32±10.30 years. Number of exacerbations was compared in both groups till 6 months. At 1st month post treatment significant difference was seen in number of exacerbations (No exacerbations: Treatment: 73% vs. Placebo: 45%, p-value=0.023) and from 2nd month till 6th month no significant difference was seen for exacerbations in both groups. For CRP level no significant difference was seen in treatment and placebo before and after treatment. i.e. After Treatment (Treatment: 18.81 vs. Placebo: 19.888, p-value=0.874). For FEV1 no significant difference was seen in treatment and placebo before and after treatment. i.e. After Treatment (Treatment: 1.55 vs. Placebo: 1.57, p-value=0.876). Mean CAT score after treatment showed significant difference for treatment and placebo groups. i.e. (Treatment: 15.17 vs, Placebo: 18.42, p-value=0.021). CAT score was significant higher in placebo group.

Conclusion: Results of this study demonstrate that addition of oral suspensions of probiotic had a significant impact on rate of exacerbation and CAT score in contrast to placebo group. However, no significant difference was seen for CRP levels after treatment in both groups.

Keywords: COPD, Probiotic, CAT score, CRP, Rate of exacerbation

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic disease that has a negative impact on quality of life of patients. COPD is the third leading cause of death worldwide and majority of deaths occurs in under developed countries[1]. COPD is characterized by a persistent inflammatory response of the lungs and airways to noxious substances, which is usually progressive and having persistent respiratory symptoms. Exacerbations and co-morbidities add to the on the whole harshness of a patient's condition[2].

A new approach to combat COPD might be the usage of probiotic. According to the World Health Organization (WHO) probiotic are defined as "organisms which, when administered alive and in adequate amounts, confer a benefit to the health of the host"[3].

Cigarette smoking activates macrophages in lungs, which triggers an inflammatory cascade. It has been demonstrated that probiotic (Lactobacillus Rahmnosus and Bifid bacterium Breve) help to suppress the activation of this inflammatory process. Thus it paves future approaches relating to application of the microbiota for the management and prevention of disease[4]. Research studies has also highlighted the Enterococcus faecalis FK-23 can diminish allergic airway inflammation by reducing T-helper 17 response[5].

Changes in microbiota composition occur after short-term antibiotic treatment and a similar effect is expected in lungs. Probiotic helps in restoring the microbial composition. It is very likely that changing the lung microbiota could affect the chronic inflammation of lung in COPD. According to some new studies commensal organisms may aid in regulation of oxidative stress, and the provocative reaction of the lungs caused by different pathogenic organisms[6].

According to the Cochrane review (2015), probiotic prophylaxis was used in a group of patients who were at risk of developing respiratory infections resulted in less number of respiratory infections and less use of antibiotics.

In COPD patient's exacerbations are usually triggered by respiratory tract infections, it is expected that probiotic treatment might reduce exacerbation rate in COPD[7]. Furthermore, a recent trial in 2017 showed improved COPD assessment test (CAT) score in COPD patients versus controls. It is imperative to investigate if this is true in local COPD patients[8].

Thus; we have designed RCT with treatment group receiving oral probiotic addition to regular treatment in order to observe any difference in frequency of exacerbation and COPD measurement test (CAT) score between treatment and control groups.

MATERIAL AND METHODS

This study was performed at Institute of TB and Chest medicine (indoor and outdoor both), Mayo Hospital Lahore. Two groups were made. One is the Intervention group were given Probiotic ampule (Enterogermina sachets containing Bacillus Clausii) 2 billion daily for 6 months. Second is the Control group in which Placebo suspension and regular treatment given. Follow-up was at baseline and then monthly till 6 months.

Follow up every month to check the primary and secondary outcome. Primary outcomes were Frequency of exacerbations, frequency of antibiotic courses for infective exacerbations and Secondary outcomes were Serum high sensitivity C-reactive protein (CRP), Pulmonary function tests (FEV1, FEV1/FVC) and CAT score (COPD assessment test).

Sample size of 80 (40 in every group) is anticipated by using 5 percent stage of worth, 90 percent command of test with

anticipated mean value placebo group as 0.6 ± 0.1 and probiotics group as 0.8±0.2[8].

$$n = 2\sigma 2 (z_1 - \alpha + z_1 - \beta)^2$$
$$(\mu_1 - \mu_2)^2$$

Sampling Technique was Simple random sampling.

Inclusion Criteria:

1 Male and female patients 30-70 years old with COPD

2 Stage II, III, and IV (GOLD criteria of COPD)

In patients with FEV1/FVC < 0.70:
GOLD 1: Mild FEV1 ≥ 80% predicted
GOLD 2: Moderate 50% ≤ FEV1 < 80% predicted
GOLD 3: Severe 30% ≤ FEV1 < 50% predicted
GOLD 4: Very Severe FEV1 < 30% predicted

3 COPD with history of 2 or more than 2 exacerbations per year

4 Stable at the time of recruitment since six weeks.

Exclusion criteria:

Pregnant or breast-feeding women,
enduring undergoing current exacerbations,
chest wall deformity,
bronchiectasis,
pulmonary fibrosis,
lung cancer,
Asthma-COPD overlap syndrome (ACOS).

These conditions can affect the lung functions, so they were excluded.

Table 1: CAT scoring

Sr No.	Question	scoring
1	I never cough 0 1 2 3 4 5 I cough all the time	
2	No Mucus in chest 0 1 2 3 4 5 Chest full of mucus	
3	Chest does not feel 0 1 2 3 4 5 Chest feel very tight Tight at all	
4	When I walk uphill or 0 1 2 3 4 5 When I walk uphill or One flight of stair I am One flight of stair I am Not breathless Very breathless	
5	No limitation of activity 0 1 2 3 4 5 Very limited activities at home At home	
6	Very confident leaving home 0 1 2 3 4 5 Not at all confident leaving home	
7	Sleep soundly 0 1 2 3 4 5 Don't Sleep soundly	
8	Lots of energy 0 1 2 3 4 5 No energy at all	
		Total score

After approval from Hospital ethical committee (888/RC/KEMU), informed consent taken, 80 patients fulfilling the inclusion/exclusion criteria are taken from the form chest medical ward, Mayo Hospital ward Lahore. Their basic demographic information (name, age, sex, registration number) was recorded. Recruitment and Randomization of patients was done. Cases were given Probiotic ampule (Enterogermina sachets containing Bacillus Clausii) and controls were given placebo. Monthly follow up was done and patients were assessed by their history of number of exacerbations and antibiotic courses used in the last month. Patients wellbeing, daily life and effect of treatment was assessed by using COPD Assessment Test (CAT) scoring.

On follow up CRP was performed. Spirometry was also performed to check the FEV1/FVC and FEV1. After data collection, data was analyzed to assess the effect of probiotics in disease severity in COPD patients. Cases and controls were counselled to avoid yogurt. Data was entered by SPSS-26. Quantitative variables like age was represented as mean + a SD. Qualitative variable like gender was represented as frequency and percentage. Comparison of two groups Placebo and probiotic group was carried out by independent sample t- test. p-value < 0.05 was in use as noteworthy

RESULTS

Mean age of patients in treatment along with in placebo assembly was 48.27±11.67 and 49.32±10.30 years.

In Treatment group 39(97.5%) were male and 1(2.5%) patient was female while in placebo group 29(72.5%) patients were male and 11(27.5%) were feminine.

Antibiotic use showed that at the end of 6 months in treatment groups only 10(25%) patients and in placebo group only 8(20%) patients were using antibiotics.

Number of exacerbations was compared in both groups till 6 months. At 1st month post treatment significant difference was seen in number of exacerbations (No exacerbations: Treatment: 73% vs. Placebo: 45%, p-value=0.023) and from 2nd month till 6th month no significant difference was seen for exacerbations in both treatment groups. Table-1

For CRP level no significant difference was seen in treatment and placebo before and after treatment. i.e. After Treatment (Treatment: 18.81 vs. Placebo: 19.888, p-value=0.874) Table-2

For FEV1 no significant difference was seen in treatment and placebo before and after treatment. i.e. After Treatment (Treatment: 1.55 vs. Placebo: 1.57, p-value=0.876) Table-3

For FEV1/FVC no significant difference was seen in treatment and placebo before and after treatment. i.e. After Treatment (Treatment: 56.04 vs. Placebo: 59.02, p-value=0.285) Table-4

Mean CAT score after treatment showed significant difference for treatment and placebo groups. i.e. (Treatment: 15.17 vs, Placebo: 18.42, p-value=0.021). CAT score was significant higher in placebo group. Table-5.

Table-1: Exacerbations in Treatment Groups

	0				1				2				3				p-value
	Treatment		Placebo		Treatment		Placebo		Treatment		Placebo		Treatment		Placebo		
Month	40		40		40		40		40		40		40		40		
1st	29	73%	18	45%	6	15%	18	45%	4	10%	4	10%	1	3%	0	0%	0.023
2nd	14	35%	17	43%	16	40%	18	45%	9	23%	3	8%	1	3%	2	5%	0.291
3rd	11	28%	14	35%	15	38%	15	38%	8	20%	9	23%	6	15%	2	5%	0.490
4th	13	33%	12	30%	15	38%	19	48%	10	25%	7	18%	2	5%	2	5%	0.792
5th	17	43%	17	43%	19	48%	15	38%	2	5%	7	18%	2	5%	1	3%	0.310
6th	28	70%	32	80%	6	15%	6	15%	5	13%	1	3%	1	3%	1	3%	0.402

Table-2: CRP before and After Treatment

	Before Treatment		After Treatment	
	Treatment	Placebo	Treatment	Placebo
N	40	40	40	40
Mean	10.31	16.20	18.81	19.88
SD	18.49	17.73	36.72	21.00
Minimum	0.60	0.10	0.50	0.90
Maximum	106.80	66.30	159.00	80.50
p-value	0.150		0.874	

Table-3: FEV1 before and after treatment

	Before Treatment		After Treatment	
	Treatment	Placebo	Treatment	Placebo
N	40	40	40	40
Mean	1.27	1.34	1.55	1.57
SD	0.34	0.37	0.63	0.59
Minimum	0.91	0.94	0.91	0.94
Maximum	2.27	2.27	3.52	2.57
p-value	0.402		0.876	

Table-4: FEV1/FVC before and after Treatment

	Before Treatment		After Treatment	
	Treatment	Placebo	Treatment	Placebo
N	40	40	40	40
Mean	51.03	52.37	56.04	59.02
SD	7.01	8.13	12.09	12.63
Minimum	34.20	43.70	34.20	43.50
Maximum	67.40	67.40	88.30	88.30
p-value	0.433		0.285	

Table-5: CAT Score before and after Treatment

	Before Treatment		After Treatment	
	Treatment	Placebo	Treatment	Placebo
N	40	40	40	40
Mean	15.02	15.17	15.17	18.42
SD	6.17	6.65	5.74	6.52
Minimum	6	4	7	8
Maximum	26	32	31	33
p-value	0.917		0.021	

DISCUSSION

Exacerbations plays an important role in the progression of disease in COPD Patients. In a study by Weinreich UM et.al. took bronchoscopic samples from stable COPD patients to see the colonization of the lower respiratory tract. Results showed that 63% of COPD patients had colonization of the airways by pathogenic bacteria which is much higher than normal population. They can cause chronic inflammation in lower respiratory tract, accelerated decline in lung functions and repeated exacerbations[9]. Probiotic supplementation in the diet of individuals with inflammatory pulmonary disease has been proven to reduce lung damage and hospitalization rates[10].

In this study we compared regular treatment plus oral suspensions of probiotic with regular treatment plus placebo in treating COPD patients in terms of rate of exacerbation, CRP level and COPD assessment test (CAT Score). Results showed no significant difference for CRP level after treatment in both treatment and placebo group. i.e. (Treatment: 18.81 vs. Placebo: 19.88, p-value=0.874) However, CAT score after treatment i.e. (Treatment: 15.17 vs. Placebo: 18.42, p-value=0.021) and rate of exacerbations at 1st moth showed significant difference between treatment and placebo group.

According to Yunes Panahi's research, supplementing with a probiotic can help relieve the symptoms of sulphur mustard (SM)-induced chronic pulmonary disease and be safe at the same time. According to his findings, FEV1/FVC improved significantly in the probiotic group, but not in the placebo group. When comparing both groups, only the CAT score (p-value 0.001) showed statistical significance (p-value 0.001). During the trial, there were no reports of adverse events.8These results are comparable with our study.

A study by Sadegh Azimzadeh Jamalkandi, showed that probiotics may be helpful in the treatment of allergic diseases. However, there was no discernible improvement in symptoms in people with asthma treated with probiotics that were taking them. Only diminutive figures of studies have been done on COPD, and the results are inconclusive as to their therapeutic efficacy. Intranasal administration may be more effective than oral administration, although more clinical trials are needed to verify this[11].

Milajerdi A, recently did a meta-analysis, and he found that probiotic can lower the stage of certain inflammatory cytokines in the blood. These cytokines include hs-CRP, TNF-a, IL-6, IL-12, and IL-4, but not IL-1B, IL-1B, IFN-g, or IL-17[12].

Use of probiotics had no effect on the CRP levels in patients of metabolic disorders. Baseline level of inflammation should be taken in account and elevated levels of probiotic would be necessary for longer time periods to affect the level of inflammatory cytokines[13].

Additional studies show that the antibacterial activity of probiotic can help prevent secondary infections, which in turn reduces inflammatory mediators and activated leukocyte generation in necrotizing pancreatitis[14].

For children with asthma, oral probiotic has been shown to reduce the bacterial consignment and inflammation in the inferior pulmonary territory, which may contain therapeutic advantages as well as prevent nosocomial pneumonia. 15

In addition, there has been an increase in interest in the possibility of probiotic and vaccines to avoid the worsening of COPD. Antimicrobial action, the strengthening of the epithelial barrier function, and immune modulation are all thought to contribute to probiotic ability to defend against pathogens. Probiotic have been revealed to decrease the regularity of lower respiratory territory illness and the colonization of harmful microorganisms in randomized controlled experiments[15].

This study has limitations like smaller sample size and single center study. Multicentric studies with large sample size and longer follow up needed to conform the results of this study are suggested.

CONCLUSION

Results of this study demonstrate that addition or oral suspensions of probiotic had a significant impact on rate of exacerbation and CAT score in contrast to placebo group. However, no significant difference was seen for CRP levels after treatment in both groups.

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