

## Original Research Article

# Effectiveness of pneumococcal vaccine in patients with chronic obstructive pulmonary disease (COPD)

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### ABSTRACT

**Background:** Pneumococcal infections are frequent cause chronic obstructive pulmonary disease (COPD) exacerbations and though various guidelines recommend the use of pneumococcal vaccines routinely to COPD patients to prevent exacerbations, the data regarding the effectiveness of this vaccine is limited and contradictory. Aims and objectives was to compare the frequency of exacerbations in patients of COPD before and after administration of pneumococcal vaccine and to find out the frequency of exacerbations in patients of COPD who are vaccinated against those who are not vaccinated as well as to study the effectiveness of pneumococcal vaccine will be analysed in respect to age, sex, Body mass index (BMI), severity of disease and other co-morbidity.

**Methods:** This was a randomized non-placebo controlled trial, conducted from September 2013 to August 2015 including total of 150 patients divided into two groups: cases and controls. The cases were administered PPV23 along with specific medication and were followed up at intervals of 3months. Exacerbations were identified based on ANTHONISEN'S criteria. Number of exacerbations in each follow-up was recorded. The data from both the groups were analysed statistically.

**Results:** After 1 year of follow up, there was significant reduction in mean number of exacerbations ( $p$  value  $<0.0001$ ) in patients with COPD in vaccinated group. PPV23 was more effective in patients with COPD of less than 65 years of age and with severe and/or very severe airflow obstruction and also in patients with lower BMI ( $\leq 21\text{kg/m}^2$ ), females and with co-morbidities.

**Conclusions:** This is an important strategy to prevent the repeated exacerbations in COPD patients particularly in severe and very severe disease groups and we support the recommendation that pneumococcal vaccine should be administered to these patients.

**Keywords:** COPD, Pneumococcal vaccine

### INTRODUCTION

COPD is a major cause of respiratory morbidity and mortality. An exacerbation of COPD is an acute event characterised by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication.<sup>1</sup> There are 3 types of exacerbations based on ANTHONISEN'S criteria.

Accordingly type 1 exacerbations were defined on the basis of three major symptoms: increased dyspnoea, sputum volume and sputum purulence. Type 2 exacerbations required two major symptoms, and type 3 exacerbations required one major symptom plus cough, wheeze or symptoms of an upper respiratory tract infection.<sup>2</sup>

The exacerbations are the source of significant suffering for patients, that add to the severity in individual patients, contribute to long-term decline in lung function, reduced physical activity and increase healthcare costs. They affect quality of life in COPD patients and also contribute to death. *Streptococcus pneumoniae* is a major cause of respiratory morbidity and mortality and commonly affects patients with comorbid illnesses, such as chronic lung and heart disease including chronic obstructive pulmonary disease. It frequently causes COPD exacerbations.

Prevention of COPD exacerbations is an important part of the management of COPD and the most recent strategy document from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) emphasises assessment of risk of exacerbations as a central part of the assessment of any COPD patient. In patients at high risk of exacerbations, management should be aimed at risk reduction.<sup>1</sup> Vaccination against influenza and pneumococcus is one such important preventive strategy. GOLD recommends the use of pneumococcal vaccination in order to prevent COPD exacerbation in all patients.<sup>1</sup> Consequently, Centers for Disease Control and Prevention (CDC) provided recommendations for the use of PPV23 among all adults aged 65 years and older, and those aged 19 to 64 years with underlying medical conditions including COPD.<sup>3</sup>

Practically all clinical studies and meta-analysis agree as to the efficacy of vaccine in the prevention of invasive pneumococcal disease. However, data regarding the effectiveness of this vaccine in reducing other more common manifestations of pneumococcal disease such as pneumonia/acute exacerbation have been inconclusive. Recommendations for pneumococcal vaccinations target people who are at high risk for invasive pneumococcal disease. However, the efficacy of pneumococcal vaccine in specific population especially elderly is doubtful.

In this context, following study was conducted in order to evaluate the clinical efficacy of the 23-valent pneumococcal polysaccharide vaccine (PPV) in patients with COPD and to correlate it with various factors associated with it.

Aims and objectives was to compare the frequency of exacerbations in patients of COPD who are vaccinated with those who are not vaccinated and to compare the frequency of exacerbations in patients of COPD before and after administration of pneumococcal vaccine. Also, to study the effectiveness of pneumococcal vaccine with respect to age, sex, BMI, severity of disease and comorbidity.

## **METHODS**

This was a randomized non-placebo controlled trial for the study of effectiveness of pneumococcal vaccine, undertaken in the department of pulmonary medicine,

SCB MCH, Cuttack from September 2013 to August 2015. The study population included all male and female patients aged more than 40 years, admitted to the ward with a diagnosis of COPD. The patients with complications like pneumothorax, lung cancer, pulmonary tuberculosis or human immunodeficiency virus infection were excluded from our study.

The study was approved by the ethical committee of this hospital. After obtaining written and informed consent, 150 patients were finally included in the study. All patients were explained about the detailed advantages and risks of pneumococcal vaccination. 75 patients who gave consent for the same, and advised for pneumococcal vaccination. Rest 75 patients unwilling for vaccination was taken as control. The Demographic, clinical, and spirometric data were taken from each patient at the beginning of the study. The overall study method involved 3 steps:

### **Recording of previous exacerbations**

At the time of admission, the previous total no. of acute exacerbations (A/E) per year of all patients (in both groups) were recorded by proper history taking and by checking their previous medical documents.

### **Intervention**

#### *Intervention group (vaccinated group)*

All patients were administered 23-valent pneumococcal capsular polysaccharide pneumococcal vaccine (a single dose of 0.5ml, intra muscular) and were prescribed disease specific medications according to current guidelines during discharge. The vaccine received was Pneumovax 23, manufactured according to methods developed by the Merck Research Laboratories. Each 0.5ml dose of vaccine contains 25 mg of each polysaccharide type in isotonic saline solution containing 0.25% phenol as a preservative.

#### *Non placebo control group (control group/nonvaccinated group)*

All patients in control group were discharged only with disease specific medication. No patients were given any vaccine or placebo.

### **Follow up**

All the patients in both the groups were followed up at intervals of 3months for 1 year, starting from the date of each patient selection (i.e. the day of pneumococcal vaccination). All patients were instructed to visit to out patient department (OPD) 3monthly upto 1 year for follow up and those who were unable to attend OPD were consulted over telephonic conversation. They were asked about number of exacerbations at each follow up and all the no. of re-exacerbations were recorded.

The exacerbations were defined by criteria laid by Anthonisen et al.<sup>2</sup> They were asked about 3 major symptoms of increased dyspnoea, sputum volume and sputum purulence. If any of them were present along with associated increased cough or wheeze or sign of upper respiratory tract infection, it was counted as an exacerbation. The primary outcome measured in our study was the number of re- exacerbations at each follow-up.

**Statistical analysis**

Data were entered into Microsoft excel and analysed using SPSS software version 21.0. Results were

displayed using appropriate graphs/tables. Appropriate tests (for dependent groups/independent groups) for statistical significance were used and a P value <0.05 was taken as the level of significance.

**RESULTS**

Out of 150 patients, 75 patients received the PPV23 (taken as cases). All patients were followed clinically for any acute exacerbation at 3 monthly intervals for 1 yr. None of the patients reported any local or systemic reaction to the vaccine. The epidemiological and clinical characteristics of the patients in the intervention and control groups are shown in Table 1 and 2.

**Table 1: Clinical parameters of cases and controls.**

	Group	No of cases	Mean	SD	Level of sig. (p)*
AGE	I	75	70.45	9.81	0.671
	II	75	67.55	9.48	
BMI	I	75	22.41	3.692	0.50
	II	75	21.96	3.302	
FEV1 %	I	75	54.68%	16.51%	0.417
	II	75	52.33%	17.92%	
No of exacerbation per yr before ADMSN	I	75	2.85	1.259	0.002
	II	75	2.12	0.944	

(\* - by unpaired t-test)

**Table 2: Comparision between Study gp (I) and Control gp (II): sex and smoking status.**

			No of cases, N=75, N%	Level of sig. (p)*
Sex	GP I	M	58 (77.33)	1.00
		F	17 (22.77)	
	GP II	M	58 (77.33)	
		F	17 (22.77)	
Addiction	Smoker	GPI	45 (60)	1.00
		GPII	44 (58.7)	
	Non-smoker	GP I	30 (40)	
		GPII	31 (41.3)	

(\* - by unpaired t-test)

Table 1 and 2 illustrates that both intervention and control groups were comparable with no significant difference in the most important aspects like age, sex, BMI and smoking habits. Patients in the intervention group averaged 70.45±9.81years while those in the control group averaged 67.55±9.48yrs.

Both the groups had also comparable forced expiratory volume at 1<sup>st</sup> second (FEV1) at the baseline evaluation. The two groups had significant difference in number of previous exacerbations at the time of admission, with the study group having 2.85 exacerbations as compared to 2.12 in the control group. This suggests that those who had more number of exacerbations had actually preferred to undergo vaccination.

On comparing the effectiveness of vaccine in the study and control groups at each follow-ups (Table 3, 4, 5 and 6), we noted a significant reduction in number of exacerbations each time in the study group as compared to the control group. At the end of 3<sup>rd</sup> month of each patient selection i.e 1<sup>st</sup> follow-up; there was 0.13 mean numbers of exacerbations in study group and 0.43 mean number of exacerbations in control group. At the end of 2<sup>nd</sup> follow-up there was 0.55 and 0.89 mean number of exacerbations in the study and control group respectively. Progressively there was increase in exacerbations with subsequent follow ups in the control/nonvaccinated group as compared to the vaccinated group. Finally, at the end of 1-year i.e 4<sup>th</sup> follow-up; there was significant difference in the mean number of exacerbations with the

study group having 1.52 and the control group having 2.24 mean number of exacerbations.

Also, there were higher deaths in control group as compared to study group at the end of follow-up (total 8 deaths in study group and 10 deaths in control group).

**Table 3: Comparison at 1<sup>st</sup> F/U (end of 3<sup>rd</sup> month).**

	Study group	Control group	Level of Sig. (p)*
Total patients	75	75	
Death during F/U	0	0	
Total no. Of A/E	10	32	<0.001
Mean	0.13±0.34	0.43±0.49	
Median (Q1Q3)	0(0-0)	0(0-1)	

(\*Mann-Whitney Test applied)

**Table 4: Comparison at 2<sup>nd</sup> F/U (end of 6<sup>th</sup> month).**

	Study group	Control group	Level of Sig. (p)*
Total patients	75	75	
Death during F/U	0	1	
Total no. of A/E	41	66	0.005
Mean	0.55±0.59	0.89±0.77	
Median (Q1Q3)	0(0-1)	1(0-1)	

(\*Mann-Whitney Test applied)

**Table 5: Comparison at 3<sup>rd</sup> F/U (end of 9<sup>th</sup> month).**

	Study group	Control group	Level of Sig. (p)*
Total patients	75	75	
Death during F/U	3	3	
Total no. of A/E	71	111	0.001
Mean	0.99±0.76	1.54±0.89	
Median (Q1Q3)	1(0-2)	1(1-2)	

(\*Mann-Whitney Test applied)

**Table 6: Comparison at 4<sup>th</sup> F/U (end of 12<sup>th</sup> month).**

	Study group	Control group	Level of Sig. (p)*
Total patients	75	75	
Death during F/U	8	10	
Total no. of A/E	102	146	<0.001
Mean	1.52±0.82	2.24±1.0	
Median (Q1Q3)	2(1-2)	2(2-3)	

(\*Mann-Whitney Test applied)

Table 7 illustrates that there is significant reduction in total as well as mean number of exacerbations in the study group after pneumococcal vaccination as compared to that before vaccination (from 2.85 before vaccination to 1.52 after vaccination). There was a decrease in mean number of exacerbations by a factor of 1.88 after 1 year of follow up (Table 3).

**Table 7: Effectiveness of vaccination in study group.**

Total patients	Total no. A/E per yr before vaccination	Mean no. Of A/E per yr	Death during F/U	Total no. of A/E after vaccination	Mean no. Of A/E per yr	Level of sig. (p)*	Decrease in mean frequency
75	214	2.85	8	102	1.52	<0.0001	1.88

(\*by paired t-test)

**Table 8: Effectiveness of vaccination in relation to age.**

Age	Total pts.	Total no. A/E per yr. before vaccination	Mean	Deaths during F/U	Total no. of A/E per yr. after vaccination	Mean	Level of sig. (p)*	Decrease in mean frequency
≤65yrs	25	83	3.32	2	37	1.52	<0.0001	2.18
>65yrs	50	131	2.62	6	65	1.47	<0.0001	1.78

(\*by paired t-test)

**Table 9: Effectiveness of vaccine in relation to sex.**

Sex	No. of pts.	Total A/E per yr. Before vaccination	Mean	F/U deaths	Total A/E per yr. After vaccination	Mean	Level of sig. (p)*	Reduction in mean frequency
Male	58	158	2.72	4	81	1.5	<0.0001	1.81
Female	17	56	3.29	4	21	1.61	0.0027	2.04

(\*by paired t-test)

**Table 10: Effectiveness of vaccine in relation to BMI.**

BMI	No. of patients	Total no. of A/E per yr. Before vaccination	Mean	Deaths during F/U	Total no. of A/E per yr. After vaccination	Mean	Level of sig. (p)*	Reduction in mean frequency
≤21kg/m <sup>2</sup>	29	93	3.2	3	38	1.46	<0.0001	2.19
>21kg/m <sup>2</sup>	46	121	2.63	5	64	1.56	0.0002	1.68

(\*-by paired t-test)

**Table 11: Effectiveness of vaccination in relation to severity.**

Severity	Total pts	Total no. of A/E per yr before vaccination	Mean	Deaths during F/U	Total no. of A/E per yr. After vaccination	Mean	Level of sig. (p)*	Reduction in mean frequency
Mild	10	15	1.5	0	12	1.2	0.434	1.25
Moderate	30	82	2.73	3	44	1.62	0.0025	1.68
Severe	31	100	3.22	5	40	1.53	<0.0001	2.1
Very severe	4	17	4.25	0	6	1.5	0.0016	2.83

(\*-by paired t-test)

**Table 12: Effectiveness of vaccination in relation to associated co-morbidities.**

	No. of patients	Total no. of A/E per yr. Before vaccination	Mean	Deaths during F/U	Total no. of A/E per yr. After vaccination	Mean	Level of sig. (p)*	Reduction in mean frequency
With comorbidities	35	123	3.51	6	39	1.34	<0.0001	2.62
Without comorbidities	40	91	2.275	2	63	1.65	0.0096	1.37

(\*-by paired t-test)

In the study group, authors also evaluated the effectiveness of pneumococcal vaccine in relation to various demographic and clinical parameters like age, sex, BMI, severity of the disease and presence of comorbidities (Table 8, 9, 10, 11 and 12). The vaccine was found to be more effective in patients who were less than 65 years of age where it resulted in a 2.18 fold decrease in mean number of exacerbations compared to a factor of 1.78 among those more than 65 years old (Table 9). It was also found to be more effective in females and in patients with a lower BMI (≤21kg/m<sup>2</sup>) (Table 10 and 11). When related to the spirometric severity of obstruction, the vaccine was found to be most effective in patients with severe and very severe disease. While patients with severe disease had a 2.1-fold decrease in mean exacerbations, patients with very severe disease had a 2.83-fold decrease (Table 11). Also, another important observation was, patients with associated co morbidities showed a greater reduction in mean exacerbations (2.62-fold) as compared to those without co morbidities, who showed a 1.37-fold decrease (Table 12).

**DISCUSSION**

*Streptococcus pneumoniae*, is an encapsulated Gram-positive bacterium that often colonizes in the nasopharynx of healthy children and adults. It can cause

illnesses varying from upper respiratory tract infections such as otitis media and sinusitis, to more aggressive and severe like pneumonia, bacterial sepsis, meningitis etc. People with impaired immune systems are susceptible to pneumococcal infection as in Young children, elderly people, patients with underlying medical conditions including chronic lung or heart disease, human immunodeficiency virus (HIV) infection, sickle cell disease, and people who have undergone a splenectomy. Vaccination is the only available tool to prevent pneumococcal disease.

Pneumococcal polysaccharide vaccines were developed more than 50 years ago and have progressed from 2-valent vaccines to the current 23-valent vaccines to prevent diseases caused by 23 of the most common serotypes of *Streptococcus pneumoniae* (PPV23) which we have used in our study.

This study revealed a significant reduction in the mean number of exacerbations at the end of 1 year of follow up in the study group as compared to control group (1.52 vs 2.24) (p value <0.0001). In fact there was a little increase in exacerbations in control group. There was also a significant decrease in exacerbations as compared to pre-vaccination (1.52 vs 1.85). Though most clinical studies and meta-analysis have shown the efficacy of

pneumococcal vaccine in the prevention of invasive pneumococcal disease in different populations, limited studies have been done in COPD patients. The data regarding the effectiveness of this vaccine in reducing acute exacerbation in COPD have been inconclusive.

Nichol et al, in a retrospective cohort study on 1898 subjects had showed that pneumococcal vaccination in elderly people with chronic lung disease was associated with significantly lower risk of hospital admissions for pneumonia and lower risk of deaths.<sup>4</sup> Franzen et al, in a study of 65 patients with long standing emphysema and/or chronic bronchitis found a reduction in the number of pneumonias at 1 year follow up compared with the year before vaccination.<sup>5</sup>

Lee TA et al, studied the impact of pneumococcal vaccination on pneumonia rates in patients with COPD and Asthma and had found that rate of pneumococcal pneumonia related hospitalizations decreased in COPD patients from 0.47 per 100 person-year in the prevaccination period to 0.37 per 100 person-years in the postvaccination period whereas controls had a small increase in rates from prevaccination (0.05 cases per 100 person-years) to postvaccination (0.8 cases per 100 person-years). The adjusted relative risk between the COPD patients and controls went from 8.02 in the prevaccination period to 3.87 in the postvaccination period. They suggested that the use of pneumococcal vaccination can reduce that disease burden in COPD and had supported the value of vaccinating COPD patients.<sup>6</sup>

In contrast, I Alfageme et al in a randomised controlled trial to evaluate the clinical efficacy of the 23-valent pneumococcal polysaccharide vaccine (PPV) in immunocompetent patients with COPD found an overall vaccine efficacy to be 24%. The study was done on 596 patients with COPD of the mean age 65.5 years, 298 of whom received PPV23. Kaplan-Meier survival analysis showed no significant differences between the group receiving the pneumococcal vaccination and the control group for time to the first episode of community-acquired pneumonia due to pneumococcus or of unknown etiology. However, it showed a significant difference with respect to the incidence of pneumococcal pneumonia between the 2 groups (vaccine: 0/298; control: 5/298; P = 0.03). Hospital admission rates and median length of hospital stays were lower in the vaccine group, but the difference was not statistically significant.<sup>7</sup>

Schembri S et al, studied the effect of both influenza and pneumococcal vaccine in patients with COPD with a mean follow up of 6.8 years between 1988 and 2006. They concluded that influenza, but not pneumococcal vaccination associated with a reduced risk of all cause mortality in COPD.<sup>8</sup>

A recent Cochrane database review that included 12 randomised controlled trials involving 2171 participants with COPD showed compared with control, the vaccine

group had a lower likelihood of developing community-acquired pneumonia, but it did not differ specifically for pneumococcal pneumonia. They did not find any difference in hospital admission or mortality from cardiorespiratory causes nor in all-cause mortality between vaccine and control. However, the likelihood of an emergency department visit for any cause was lower in one study for vaccine than for control and the likelihood of a COPD exacerbation was significantly reduced.<sup>9</sup>

In this study, on correlation with various factors, the vaccine was found to be more effective in patients who were less than 65 years of age where it resulted in 2.18 fold decrease in mean no. Of exacerbations as compared to a factor of 1.78 among those who were more than 65 years of old. This was similar to the study by Alfageme I et al where the vaccine had an efficacy of 76% in patients of <65 years of age.<sup>7</sup> Again the vaccine was found to be most effective in patients with severe and very severe disease. Patients with severe disease had a 2.1 fold decrease in mean exacerbations while patients with very severe disease had a 2.83 fold decrease. Alfageme I et al, had also shown a higher vaccine efficacy of 91% in those who had severe airflow obstruction.<sup>7</sup> In addition our study found a significant reduction in exacerbations in females, those associated with comorbidities and those with lower BMI ( $\leq 21 \text{ kg/m}^2$ ). Our study was at par with Walter JAE et al, who concluded that vaccination reduced the likelihood of a COPD exacerbation, and moderate-quality evidence suggests the benefits of pneumococcal vaccination in people with COPD.<sup>10</sup>

So, this study shows that the protective efficacy of 23 serotype PPV in COPD patients is linked to five factors-age (<65yr), female sex, BMI ( $\leq 21 \text{ kg/m}^2$ ), severity of disease (severe and very severe obstruction) and associated comorbidities as can be seen from the reduction exacerbation frequencies.

This study had a limitation that there was lack of a blind placebo comparison group so that any bias would not arise.

## CONCLUSION

This study analysed the effectiveness of the pneumococcal vaccine in a cohort of patients with a clinical suspicion and spirometric diagnosis of COPD. There was significant reduction in COPD exacerbations after pneumococcal vaccination (PPV23). It was more effective in patients aged <65 years, females, low BMI ( $< 21 \text{ kg/m}^2$ ), stage III and IV, and in patients associated with co-morbidities like cor pulmonale, diabetes mellitus, hypertension etc.

So, according to this study, this may be an important management strategy to prevent the recurrent exacerbations in COPD patients particularly in severe and very severe disease groups and to improve the quality of

living and to extend the survival period in COPD patients. Authors therefore agree on the recommendation that pneumococcal vaccine should be administered to these patients, independent of the cost effectiveness analysis. However, there are very less number of randomised controlled trials which have correlated the effectiveness of the vaccine in COPD patients to various demographic and clinical factors like age, sex, severity etc as in our study. So, larger well designed studies are required to prove any such association.

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