



A STUDY OF EFFECT OF VACCINATION (PNEUMOCOCCAL&/INFLUENZA) ON EXACERBATION RATES IN PATIENTS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Medicine

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ABSTRACT

Background: Exacerbations form a major component of the socioeconomic burden related to COPD, and are associated with greater decline in health status. Since tracheobronchial infections are most common cause of exacerbation, this study is conducted to assess the effectiveness of vaccination status. **Methods:** 50 patients with COPD were recruited from the out-patient + inpatient clinic between January 2019 and May 2020. Subject demographic data, COPD staging, smoking status, co-morbidities, previous history of exacerbations were recorded. They were divided into two groups: Group A (Vaccinated) and Group B (Non-vaccinated). Group A further divided into Group A1 (Pneumococcal vaccine) and A2 (Pneumococcal+ Influenza) with 17 and 08 patients respectively. Vaccination status, and COPD-related emergency or hospital admissions triggered by tracheobronchial infections over 1 y after administration of both influenza and pneumococcal vaccines were noted. **Results:** 50 male patients with Mean age $\pm$ SD 54.96 $\pm$ 8.12 were enrolled in the study. Vaccinated patients (Group A1 and Group A2) had highly significant reduction in both exacerbation and hospitalization rates ($P < 0.01$) compared to non-vaccinated (Group B). Amongst Group A1, there was highly significant reduction in exacerbation rate in patients with age < 65 years, Stage III COPD and non-smokers ($P < 0.01$) compared to patients with age > 65 years, other stages of COPD and smokers respectively. **Conclusion:** The significant reduction in exacerbation rate suggests role of vaccination in prevention of exacerbations. Hence, Physicians should recommend both influenza and pneumococcal vaccines to all patients with COPD according to GOLD guidelines to reduce exacerbations.

KEYWORDS

Chronic Obstructive Pulmonary Disease (COPD), Pneumococcal vaccine, Influenza vaccine, exacerbation.

INTRODUCTION:

Chronic Obstructive Pulmonary Disease (COPD) is a common respiratory disease which may be punctuated by periods of acute worsening of respiratory symptoms, called exacerbations. Exacerbations of COPD are associated with worsening of airflow obstruction, hospitalization, reduced quality of life, disease progression, death, and ultimately, substantial healthcare-related costs[1]. At least 70% of COPD exacerbations are infectious in origin, with respiratory viruses identified in approximately 30% of cases[2]. Influenza is a frequent cause of exacerbations of chronic obstructive pulmonary disease. Prevention of COPD exacerbations is an important part of the management of COPD and most recent strategy document from the Global Initiative for COPD emphasizes assessment of risk of exacerbations as a central part of assessment of any COPD patient[3]. The most common vaccines given to patients with COPD are for the prevention of pneumococcal and influenza infections, which have high exacerbation rates[4]. Influenza vaccination reduces serious illness and death in COPD patients. The 23-valent pneumococcal polysaccharide vaccine (PPSV23) has been shown to reduce the incidence of community acquired pneumonia in COPD patients aged < 65 years with an FEV1 $< 40\%$ predicted and in those with comorbidities[5].

AIMS & OBJECTIVES:

- To compare the exacerbation and hospitalization rates in vaccinated & non-vaccinated patients of Chronic Obstructive Pulmonary Disease.
- To compare the effectiveness of vaccination on exacerbation rate in mild, moderate, severe and very severe stages of Chronic Obstructive Pulmonary Disease (GOLD 2019)

MATERIALS AND METHODS:

A prospective study was conducted in Department of Respiratory Medicine, AMC MET Medical College, Sheth LG Hospital, Ahmedabad during the period from January 2019 to May 2020. Patients of Chronic Obstructive Pulmonary Disease (Outdoor+ Indoor patients) already on standard treatment according to GOLD 2019 guidelines were included in the study after informed consent.

Inclusion Criteria:

- Patients with Chronic Obstructive Pulmonary Disease having Post-Bronchodilator FEV1/FVC ratio < 0.7 according to GOLD 2019 guidelines.
- Patients willing to participate in the study.

Exclusion Criteria:

- Patients having other co-morbidities (Asthma, Bronchiectasis, Acute infectious diseases, Active Tuberculosis, Carcinoma)
- Patients having hypersensitivity to vaccine components, severe complications of previous vaccination.
- Patients vaccinated against pneumococcal within 3 years.
- Previous vaccination against H. influenza type B infection.

Out of 50 patients of COPD enrolled in the study, 25 patients were vaccinated and remaining 25 patients not willing/not affording for vaccination but fulfilling the inclusion criteria were included in the study. Patients were categorized according to the severity of COPD into Mild (FEV1 $\geq 80\%$), Moderate (FEV1 50-79%), Severe (FEV1 30-49%) and Very severe (FEV1 $< 30\%$) stages of COPD. Patients were divided into two groups based on the vaccination status. Group A included patients willing for vaccination [Influenza &/ Pneumococcal] and Group B included those not willing for vaccination. Group A was further divided into two subgroups: Group A1 (Only Pneumococcal vaccine) and Group A2 (Pneumococcal+ Influenza vaccine). There were 17 patients in Group A1 and 8 patients in Group A2.

All patients were asked detailed history including the past history of exacerbations (frequency and severity) and underwent routine physical examination and baseline tests such as:

- Hemoglobin level,
- Total White blood cell count,
- Random blood sugar,
- Renal function tests,
- Liver function tests,
- Pulmonary Function test,
- Chest X ray (PA VIEW).
- Sputum for AFB, Sputum for culture and sensitivity.

Vaccination:

- After taking the universal aseptic precautions, Pneumococcal polysaccharide vaccine (PPSV23) 0.5ml (1 dose) was administered with a 24 gauge needle intramuscularly at Left deltoid region in majority and in Left Antero-lateral aspect of thigh region in few in the injection room of the hospital.
- Inactivated Influenza vaccine 0.5ml (1 dose) was also administered intramuscularly with a 24 gauge needle but at different site (Right deltoid/Right anterolateral aspect of thigh) after taking the aseptic universal precautions in the same visit in injection room of the hospital.

Follow up visits:

- Patients of both the groups were explained about consulting hospital immediately if they had fever, purulent sputum, worsening dyspnea &/ cough at any given point of time over a period of 1 year and regular monthly outdoor follow up visits. Patients were also counselled to continue the standard pharmacotherapy according to GOLD guidelines throughout the study. When patient developed exacerbation, then according to the severity of the exacerbation (GOLD 2019), Mild (treated with SABDs only), Moderate (treated with SABDs plus antibiotics and/or oral corticosteroids) or

Severe (patient requires hospitalization or visits the emergency room), they were treated on outdoor or indoor basis accordingly.

All the patient data were recorded in the proforma. Then data was compiled in Microsoft Excel Sheet and analyzed using SPSS software (20.0 version) and following statistical tests:

- The Kolmogorov-Smirnov test was used for normal distribution of variables.
- The Paired t-test, unpaired t-test and one-way ANOVA test were used for normally distributed data.
- Wilcoxon Sign Rank Test, Mann-Whitney U test and Friedman test were used for not normally distributed data.

RESULTS:

50 patients were enrolled in the study. All were male (100%) and the mean age $\pm$ SD was 54.96 ± 8.12 . According to the GOLD 2019 classification, 12 subjects (24%) were in stage I, 21 subjects (42%) in stage II, 14 subjects (28%) in stage III, 3 subjects (6%) in stage IV of COPD. In Group A, 17 were non-smokers, 5 ex-smokers and 3 current smokers, whereas in Group B, 7 non-smokers, 4 ex-smokers and 14 current smokers. All patients had BMI within normal range except one patient with low BMI (17.5 kg/m^2). Out of 50 patients, 16 patients (32%) had one and/or more co-morbidities (26% Hypertension, 12% Diabetes Mellitus, 2% Ischemic Heart Disease).

Table 1: Comparison of exacerbation and hospitalization rate before and after vaccination amongst three groups and variables.

Variables	No. of exacerbation/ year			No. of Hospitalization/ year		
	Before Vaccination	After Vaccination		Before Vaccination	After Vaccination	
	Mean $\pm$ SD	Mean $\pm$ SD	P value	Mean $\pm$ SD	Mean $\pm$ SD	P value
Age						
<65 (n=19)	1.53 ± 0.51	0.63 ± 0.50	HS	0.84 ± 0.37	0.47 ± 0.513	S

65 or >65 (n=6)	1.83 ± 0.983	1.17 ± 0.753	S	1.17 ± 0.75	0.50 ± 0.55	S
GOLD Category						
GOLD I (n=5)	1.00 ± 0.01	0.40 ± 0.55	NS	0.60 ± 0.55	0.40 ± 0.55	NS
GOLD II (n=9)	1.56 ± 0.53	0.56 ± 0.53	S	0.89 ± 0.33	0.22 ± 0.44	S
GOLD III (n=11)	1.91 ± 0.70	1.09 ± 0.54	HS	1.09 ± 0.54	0.73 ± 0.47	S
Smoking						
Non-smoker (n=17)	1.35 ± 0.49	0.59 ± 0.51	HS	0.76 ± 0.44	0.29 ± 0.47	HS
Ex-smoker (n=5)	1.80 ± 0.45	0.80 ± 0.45	NS	1.00 ± 0.40	0.80 ± 0.45	NS
Smoker (n=3)	2.67 ± 0.58	1.67 ± 0.59	NS	1.67 ± 0.58	1.00 ± 0.00	NS
Pneumococcal vaccination (Group A1)						
Yes (n=17)	1.47 ± 0.72	0.94 ± 0.56	HS	0.88 ± 0.60	0.59 ± 0.51	NS
No (n=25) (Group B)	1.96 ± 0.93	2.40 ± 0.96	S	1.28 ± 0.84		NS
Influenza + Pneumococcal vaccination (Group A2) (n=8)	1.88 ± 0.35	0.38 ± 0.52	S	1.00 ± 0.00	0.25 ± 0.46	S
BMI (kg/m^2) 18.5-24.99 (n=24)	1.63 ± 0.65	0.75 ± 0.61	HS	0.92 ± 0.50	0.50 ± 0.51	HS
Comorbidities:						
Hypertension (n=10)	2.10 ± 0.57	1.00 ± 0.67	HS	1.20 ± 0.42	0.60 ± 0.52	S

*S = <0.05, *HS = <0.01, *NS = >0.05

*n = No of patients.

*SD = Standard deviation

Group A (Vaccinated)

- When exacerbation rate of Group A1 (Mean $\pm$ SD is 0.94 ± 0.56) was compared with Group A2 (Mean $\pm$ SD is 0.38 ± 0.52), it was found to be significantly reduced ($P < 0.05$); whereas hospitalization rate (Mean $\pm$ SD 0.59 ± 0.51) compared to Group A2 (0.25 ± 0.46) was insignificant ($P > 0.05$). Hence, immunization with both vaccines is more effective in reducing exacerbation and hospitalization rate.
- There was highly significant reduction in exacerbation rate in patients with age <65 years ($P \text{ value} < 0.01$) compared to patients with age >65 years. Hence all COPD patients with age <65 years must be vaccinated with pneumococcal vaccine.
- There was highly significant reduction in exacerbation rate ($P \text{ value} < 0.01$) in severe stage (FEV1 30-49%) of COPD and significant ($P \text{ value} < 0.05$) in moderate stage (50-79%) of COPD compared to mild (FEV1 $\geq 80\%$) stage ($P \text{ value} > 0.05$).
- There was highly significant reduction in exacerbation and hospitalization rate ($P \text{ value} < 0.01$) in non-smokers compared to ex-smokers and current smokers ($P \text{ value} > 0.05$). Hence, smoking has negative correlation with exacerbation rate.

Group B (Non-vaccinated)

- When exacerbation (Mean $\pm$ SD is 0.94 ± 0.56) and hospitalization rate (Mean $\pm$ SD is 0.59 ± 0.51) of Group A1 were compared with Group B (Mean $\pm$ SD is 2.40 ± 0.96 and 1.40 ± 0.87 respectively) both had highly significant reduction ($P < 0.01$).
- When exacerbation (Mean $\pm$ SD is 0.38 ± 0.52) and

hospitalization rate (Mean $\pm$ SD is 0.25 ± 0.46) of Group A2 were compared with Group B(Mean $\pm$ SD 2.40 ± 0.96 and 1.40 ± 0.87 respectively) both had highly significant reduction($P < 0.01$). Hence, vaccination reduces exacerbation and hospitalization rates significantly.

DISCUSSION:

According to GOLD guidelines 2019, Influenza vaccination is recommended for all patients with COPD. PCV13 and PCV23 are recommended for all patients > 65 years of age, and in younger patients with significant comorbid conditions including chronic heart or lung disease[5].

In present study, as shown in Table 2, Mean age $\pm$ SD is 54.96 ± 8.12 which is not similar with Thitta Mohanty et al study with Mean age $\pm$ SD 70.45 ± 9.81 . Patients in the intervention group averaged 70.45 ± 9.81 years while those in the control group averaged 67.55 ± 9.48 yrs. 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 which is comparable with the present study.

Table 2: Comparison of Exacerbation rate, Hospitalization rate and various variables with other studies.

	Pinar Cimen et al[4]	Ulku Aka Akturk et al[6]	Marcela Alves et al [7]	Thitta Mohanty et al[8]	Zoe Kopsaftis et al[9]	Julia Ae Walters et al[10]	Present study
Mean age $\pm$ SD (years)	61.5	66.3 ± 9.3	-	70.45 ± 9.81	67.3	66	54.96 ± 8.12
Exacerbation rate	$P < 0.001$	-	$P = 0.415$	$P < 0.0001$	Mean Deviation MD-0.37, 95% CI -0.64 To -0.11; $P = 0.006$	OR 0.60, 95% CI 0.39 TO 0.93	$P < 0.05$
Hospitalization rate	$P < 0.02$	-	$P = 0.415$	-	$P = 0.52$	RR 0.84, 95% CI 0.26 TO 2.71	$P < 0.05$
GOLD STAGING:							
GOLD I	5.7%	4.2%		1.33%			24%
GOLD II	25%	40.8%		40%			42%
GOLD III	38.6%	36.6%		41.33%			28%
GOLD IV	30.7%	18.5%		5.33%			6%
Co-morbidities:							
Hypertension	-	60.8%	-	46.67%	-	-	32%
Diabetes Mellitus		37%		-			26%
Cardiovascular disease		13.9%		-			12%
		23.1%		-			2%

In present study, 24% patients were in Stage I (Mild) , 42% in Stage II (Moderate), 28% in Stage III (Severe) and 6% in Stage IV (Very severe) of COPD. Stage II and Stage III patients are comparable to Ulku Aka Akturk et al and Thitta Mohanty et al study.

In present study , 26% had hypertension, 12% had diabetes mellitus and 2% had cardiovascular disease which is comparable with Ulku Aka Akturk et al (37% hypertension, 13.9% diabetes mellitus) and Thitta Mohanty et al in which 46.67% patients had comorbidities. In

patients with hypertension, exacerbation and hospitalization rate was significantly decreased after vaccination.

In present study, both exacerbation and hospitalization rates are significantly decreased ($P < 0.05$) after vaccination which is comparable to Marcela Alves et al and Zoe Kopsaftis et al. Hence, vaccination is effective in reducing exacerbation and hospitalization rates.

In present study, both exacerbation and hospitalization rates were significantly decreased in non-smokers after vaccination. However, there are limited studies showing efficacy of vaccination in smokers.

CONCLUSION:

In our study, significant reduction in exacerbation rate and hospitalization has been found in the vaccinated patients specifically more in patients with age < 65 years, non-smokers and moderate-severe COPD compared to non-vaccinated patients, patients with age > 65 years, current smokers and mild stage of COPD. Hence, present study favors GOLD guidelines vaccine recommendation in every COPD patients in order to reduce exacerbation rates which ultimately reduces hospital stay and cost of treatment.

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