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RESEARCH ARTICLE
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The comparison of exacerbation and pneumonia before and after conjugated pneumococcal vaccination in patients with chronic obstructive pulmonary disease, and the effect of inhaled corticosteroid use on results

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ABSTRACT

The comparison of exacerbation and pneumonia before and after conjugated pneumococcal vaccination in patients with chronic obstructive pulmonary disease, and the effect of inhaled corticosteroid use on results

Introduction: Pneumococcal infections and exacerbations are important causes of mortality and morbidity in chronic obstructive pulmonary disease (COPD). The use of inhaled corticosteroids and pneumococcal vaccination are suggested for the control of the disease progression and exacerbations. The aim of this study is to assess the effect of pneumococcal conjugate vaccine on pneumonia and exacerbation in COPD patients using inhaled corticosteroids (ICSs). The secondary aim is to analyze the effect of ICS use and different ICS types, if administered, on exacerbation and pneumonia incidence in the study population.

Materials and Methods: Medical records of 108 adult patients with COPD who were vaccinated with the pneumococcal conjugate vaccine (PCV13) were retrospectively evaluated. The number of acute exacerbations and pneumonia within one year before and after vaccination were evaluated in all included COPD patients. The comparison analysis was also performed based on the ICS types.

Results: There were statistically significant differences between the mean numbers of pneumonia and exacerbations before and after vaccination ($p < 0.05$). There were no significant differences in the mean pneumonia attacks and acute exacerbations between patients using ICS and not using ICS ($p > 0.05$).

Conclusion: This study revealed that PCV13 provides a significant decrease in both exacerbation and pneumonia episodes in COPD patients. On the other hand, the use of ICSs and the types of ICSs were not found to have adverse effects on pneumonia and acute exacerbations in vaccinated COPD patients.

Key words: Chronic obstructive pulmonary disease; vaccination; pneumococcal conjugate vaccine; inhaled corticosteroids; vaccination in chronic obstructive pulmonary disease

ÖZ

Kronik obstrüktif akciğer hastalığı olan hastalarda konjuge pnömokok aşısı öncesi ve sonrası alevlenme ve pnömoni sıklığının karşılaştırılması ve inhale kortikosteroid kullanımının sonuçlara etkisi

Giriş: Kronik obstrüktif akciğer hastalığında (KOAH) pnömokok enfeksiyonları ve alevlenmeleri önemli mortalite ve morbidite nedenleridir. Hastalığın ilerlemesi ve alevlenmelerinin kontrolü için inhale kortikosteroid kullanımı ve pnömokok aşısı önerilmektedir. Bu çalışmanın amacı inhale kortikosteroid (İKS) kullanan KOAH hastalarında konjuge pnömokok aşısının pnömoni ve alevlenme üzerindeki etkisini değerlendirmektir. İkincil amaç ise, İKS kullanımının varlığının ve kullanılıyorsa farklı İKS tiplerinin aşılama öncesi ve sonrası dönemde alevlenme ve pnömoni insidansına etkisini de analiz etmektir.

Materyal ve Metod: Konjuge pnömokok aşısı (PCV13) uygulanmış KOAH tanılı 108 erişkin hastanın tıbbi kayıtları retrospektif olarak değerlendirildi. Dahil edilen tüm KOAH hastalarında aşılamadan önceki ve sonraki bir yıl içindeki akut alevlenme ve pnömoni sayıları analiz edildi. Ek olarak alevlenme ve pnömoni insidansına etkisi açısından İKS tipleri ile ilgili karşılaştırma analizi de yapıldı.

Bulgular: Aşılama öncesi ve sonrası ortalama pnömoni ve alevlenme sayıları arasında istatistiksel olarak anlamlı farklılıklar vardı ($p < 0,05$). İKS kullanan ve kullanmayan hastalar arasında ortalama pnömoni atakları ve akut alevlenmeler açısından anlamlı fark yoktu ($p > 0,05$).

Sonuç: Bu çalışmada, PCV13'ün KOAH hastalarında hem alevlenme hem de pnömonide anlamlı bir azalma sağladığı gösterilmiştir. Öte yandan, aşı KOAH hastalarında İKS kullanımının ve kullanan hastalarda farklı İKS tiplerinin pnömoni ve akut alevlenmeler üzerinde olumsuz etkisi bulunmamıştır.

Anahtar kelimeler: Kronik obstrüktif akciğer hastalığı; aşılama; konjuge pnömokok aşısı; inhale kortikosteroidler; kronik obstrüktif akciğer hastalığında aşılama

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the most important health problems with high morbidity and mortality rates. Currently, COPD is considered to be the fourth leading cause of death worldwide, however, it is expected to be the third as of 2020. At least three million people died of COPD in 2012, accounting for 6% of all deaths globally (1). On the other hand, pneumonia is the third most frequent cause of death according to the 2019 WHO report (2).

Acute exacerbations and infections increase the mortality in COPD patients. Two out of three acute exacerbations in COPD are associated with viral or bacterial respiratory tract infections, although there are various reasons for COPD exacerbations. In COPD, mucociliary clearance is insufficient therefore, bacteria and viruses can easily proliferate in respiratory tract mucosa. For this reason, COPD patients are highly vulnerable to lower respiratory tract infections. *Streptococcus pneumoniae* is the most common bac-

teria isolated from adult cases of community-acquired pneumonia (CAP), which is well-known as the most common pulmonary infectious disease. In the United States, it is reported that pneumococcal pneumonia is responsible for approximately 30% of adult CAP cases and at least 400.000 hospitalizations each year (3). An analysis of data from the Global Burden of Disease Study revealed that *S. pneumoniae* was the most prominent infectious agent of the lower respiratory tract in 2016 causing high morbidity and mortality worldwide. It is also reported that *S. pneumoniae* caused more deaths (1.189.937 deaths) compared to other lower respiratory infection agents in 2016 (4). Shoji et al. reported that *S. pneumoniae* was isolated in 15% of lower respiratory infections in COPD patients (5). Additionally, the use of inhaled corticosteroids may increase the pneumonia risk in COPD (6).

According to GOLD 2022, 13-Valent Pneumococcal Conjugate Vaccine (PCV13) or 23-Valent Pneumococcal Polysaccharide Vaccine (PPSV23) are recommended for COPD patients to reduce CAP inci-

dence, invasive pneumococcal infections, and bacteremia. Vaccination strategies against pneumococcal infection in COPD were shown to be effective healthcare interventions for reducing invasive pneumococcal disease in all age groups, and these strategies have been established in most of the European countries for elderly COPD patients and the patients with severe comorbidities (7). In the GOLD 2022 guidelines, individuals over 65 years of age are recommended to be vaccinated with pneumococcal vaccines, PCV13 and PPSV23. Also, patients below 65 years of age who have comorbidities such as chronic lung, cardiac or liver diseases, and diabetes mellitus are recommended to be vaccinated with PPSV23 (8). A recent randomized-controlled study reported that PCV13 reduced the pneumococcal infection by 75% for at least four years in COPD patients over 65 years of age (9).

The purpose of this study is to investigate the effect of the PCV13 vaccine on pneumonia and exacerbation frequency in COPD patients using ICS, and also to analyze whether ICS type is effective on pneumonia and exacerbation rates in COPD patients who were vaccinated with PCV13.

MATERIALS and METHODS

This retrospective clinical study was carried out at a tertiary academic center after approval by the institutional review board (Approval number and date: 8528/07.11.2018) and in accordance with the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all subjects.

Patient Selection

In this study, medical records of 218 adult patients (>18 years) with COPD (functional expiratory volume-1 (FEV₁)/forced vital capacity (FVC)< 70%, post-bronchodilator) who were vaccinated by PCV13 (Prevnar 13®, Wyeth Pharmaceuticals LLC. Marketed by Pfizer Inc., New York City, New York, USA) between May 2018 and September 2018 and using ICS for at least one year before the date of vaccination, were retrospectively evaluated. A single dose (0.5 mL) of PCV13 vaccine was given by intramuscular injection using a 22-gauge needle into the deltoid muscle of the upper arm. Patients were excluded from the study if they had any of the following conditions: Lung cancer, interstitial lung disease, asthma, bronchiectasis, or missing medical records. A hundred ten patients who met one or more exclusion

criteria were excluded from the study and the remaining 108 patients were included. All patients were of the Caucasian race and Turkish ethnicity. None of the patients had concomitant drug use except inhaled corticosteroids and long-acting beta-agonists.

Outcome Measures

The number of acute exacerbation and pneumonia episodes within one year before and after vaccination was evaluated in all included COPD patients. In addition, the patients were grouped, and these groups were compared based on the type of inhaled corticosteroids being used. The acute exacerbation and pneumonia numbers within one year before and after vaccination were also compared based on the type of ICS used. In addition, tobacco consumption, comorbidities, use of nebulizers, FEV₁ scores were evaluated.

The aim of this study was to analyze the effect of PCV13 vaccination on COPD exacerbation and pneumonia frequency and to assess the effect of ICS use and different types of inhaled corticosteroids (budesonide, fluticasone propionate, and fluticasone furoate) on exacerbation and pneumonia in vaccinated COPD patients.

Statistical Analysis

Statistical analysis was performed using computer software (SPSS version 25.0; SPSS Inc., Chicago, Illinois, USA). Levene test was used to evaluate whether the data had homogeneous variance, and Shapiro-Wilk test was used to analyze whether the variables with homogeneous variance showed normal distribution. Independent samples t test was used for the comparison of categorical data, while Wilcoxon and Mann-Whitney U tests were used for the analysis of non-parametric variables based on the distribution pattern. The independent-samples t test was used to analyze the ICS use on exacerbation and pneumonia before and after vaccination. The one-way ANOVA test was used to analyze the effect of ICS type on exacerbation and pneumonia before and after vaccination. Data were expressed as mean (standard deviation; SD), percent (%), minimum-maximum, and median (interquartile range; IQR), where appropriate. $p < 0.05$ was considered to be statistically significant. For post hoc analyses, $p < 0.016$ was considered to be statistically significant due to Bonferroni correction.

RESULTS

Ninety patients (83.3%) were male, and eighteen patients (16.73%) were female. The mean age was 65.7 ± 9.8 years. The mean body mass index was 23.6 ± 4.1 kg/m². Sixty-six out of 108 patients (61.1%) were ex-smokers, 39 (36.1%) were active smokers and three (2.8%) were non-smokers. Nineteen patients (21.1%) had a history of nebulizer usage (with budesonide). The mean FEV₁ score was $51.8\% \pm 18.4\%$ (ranged between 20-108%). Budesonide, fluticasone furoate, and fluticasone propionate were used by 41 patients (38%), 24 patients (22.2%), and 25 patients (23.1%), respectively. Eighteen patients (16.7%) did not use any inhaled corticosteroids. Clinical and demographic data of all patients are presented in Table 1.

Among all patients, the mean number of exacerbations was 2 ± 1.9 (ranged, 0-15) and 1.6 ± 1.7 (ranged, 0-13) within a year before and after PCV13 vaccination, respectively. The difference between the mean number of exacerbations before and after vaccination was statistically significant ($p=0.005$). Among all patients, the mean number of pneumonia episodes was 1.1 ± 1.3 (ranged, 0-8) and 0.7 ± 1.1 (ranged, 0-6) within one year before and after PCV13 vaccination, respectively. There was a statistically significant difference between the mean number of pneumonia episodes before and after vaccination ($p=0.004$). In patients using ICS, there were

significant differences between the mean exacerbation and pneumonia episodes one year before and after vaccination ($p=0.001$ and 0.007 for exacerbation and pneumonia, respectively). In patients not using ICS, there were no significant differences between the mean exacerbation and pneumonia episodes one year before and after vaccination ($p=0.779$ and 0.363 for exacerbation and pneumonia, respectively). The comparisons of the mean number of exacerbations and pneumonia episodes in all patients and according to ICS use in the one-year period before and after vaccination are presented in Table 2.

There were statistically significant decreases in mean post-vaccination exacerbation and pneumonia numbers compared to the pre-vaccination period in the fluticasone propionate group ($p=0.004$ and 0.003 for exacerbation and pneumonia, respectively). There was a statistically significant decrease only in the mean post-vaccination pneumonia episodes compared to the pre-vaccination period in the fluticasone furoate group ($p=0.047$). The comparisons of mean exacerbation and pneumonia numbers between pre- and post-vaccination regarding ICS type are presented in Table 3.

The independent-samples t test for exacerbation profile (pre- and post-vaccination period) revealed that there was no significant difference between patients using ICS and not using ICS ($p=0.105$).

Table 1. Clinical and demographic data of the patient series

Parameter	Value (number) (%)
Age (years)	65.7 ± 9.8
Male/Female	90/18
Tobacco Consumption	
• Non-Smoker	3 (2.7%)
• Active-Smoker	39 (35.4%)
• Ex-Smoker	66 (61.9%)
Use of Nebuliser (Among the patients using ICS ^a)	
• No	71 (78.9%)
• Yes	19 (21.1%)
Inhaled Corticosteroid	
• None	18 (16.7%)
• Fluticasone Propionate	25 (23.1%)
• Fluticasone Furoate	24 (22.2%)
• Budesonide	41 (38%)
Mean FEV ₁ % ^b (min-max)	$51.8 \pm 18.4\%$, (20-108%)

^aInhaled corticosteroid, ^bForced expiratory volume at the end of the first second.

Table 2. The comparisons of the mean number of exacerbations and pneumonia in all patients and according to ICS use in the one year period before and after vaccination

	All Patients	Patients using ICS ^a (n= 90)	Patients not using ICS (n= 18)
Mean Exacerbation Before Vaccination (min-max)	2 ± 1.9 (0-15)	2.2 ± 2 (0-15)	1.3 ± 1.2 (0-4)
Mean Exacerbation Following Vaccination (min-max)	1.6 ± 1.7 (0-13)	1.6 ± 1.8 (0-13)	1.4 ± 1.5 (0-4)
p value	0.005	0.001	0.779
Mean Pneumonia Before Vaccination (min-max)	1.1 ± 1.3 (0-8)	1.1 ± 1.3 (0-8)	0.9 ± 0.9 (0-3)
Mean Pneumonia Following Vaccination (min-max)	0.7 ± 1.1 (0-6)	0.7 ± 1.2 (0-6)	0.6 ± 0.9 (0-3)
p value	0.004	0.007	0.363

^aInhaled corticosteroid.

Table 3. The comparison of mean exacerbation and pneumonia numbers between pre and post-vaccination period according to ICS type

	Fluticasone Propionate (n= 25)	Fluticasone Furoate (n= 24)	Budesonide (n= 41)
Mean Exacerbation Before Vaccination (min-max)	2.7 ± 1.8 (0-7)	2.4 ± 2.9 (0-15)	1.7 ± 1.4 (0-5)
Mean Exacerbation Following Vaccination (min-max)	1.6 ± 1.7 (0-8)	1.8 ± 2.5 (0-13)	1.6 ± 1.3 (0-6)
p value	0.004	0.139	0.330
Mean Pneumonia Before Vaccination (min-max)	1.4 ± 2 (0-8)	1.2 ± 0.8 (0-3)	1 ± 1 (0-4)
Mean Pneumonia Following Vaccination (min-max)	0.6 ± 1.1 (0-4)	0.8 ± 1.4 (0-6)	0.8 ± 1.1 (0-4)
p value	0.003	0.047	0.570

Table 4. The comparisons of exacerbation and pneumonia differences between the patients using and not using ICS and ANOVA test for the effect of ICS types

		Patients using ICS ^a (n= 90)	Patients not using ICS (n=18)	p value
Mean Exacerbation	Pre-vaccination	2.2 ± 2	1.3 ± 1.2	0.105
	Post-vaccination	1.6 ± 1.8	1.4 ± 1.5	
Mean Pneumonia	Pre-vaccination	1.1 ± 1.3	0.9 ± 0.9	0.669
	Post-vaccination	0.7 ± 1.2	0.6 ± 0.9	
ANOVA test for ICS types		Exacerbation	Pneumonia	
p value		0.053	0.158	

^aInhaled corticosteroid.

Additionally, the independent-samples t-test for pneumonia profile pre- and post-vaccination period revealed that there was no significant difference between patients using ICS and not using ICS ($p=0.669$). By using the one-way ANOVA test, the effect of ICS type difference on exacerbation and pneumonia was analyzed and post hoc pairwise comparisons were performed. There were no statistically significant differences in the decrease in exacerbations and pneumonia episodes among three ICS groups ($p=$

0.053 and 0.158 for exacerbation and pneumonia, respectively). None of the pairwise comparisons of ICS types were statistically significant ($p>0.016$). The comparisons of exacerbation and pneumonia between ICS users and non-users and ANOVA analysis for ICS types are presented in Table 4.

DISCUSSION

COPD is a non-curable chronic disease that affects not only individuals but the community and is a big

burden for healthcare systems worldwide. Long-term treatment duration and hospitalization requirements due to pneumonia are major problems for both patients and the medical team, especially in patients over 65 years of age and with poor COPD control. Today, in COPD, treatment modalities mostly aim to get the disease under control. Furthermore, vaccination seems to be the most reasonable method for reducing the unfavourable effects of pneumococcal infections on clinical and economical burdens in COPD patients (10). Herein, the main questions that build the arguments of this study are as follows:

1. Does pneumococcal vaccination reduce the exacerbation and pneumonia episodes in COPD patients in short-term (one year) follow-up?
2. Do the ICSs increase the risk of acute pneumonia and exacerbation in COPD patients, even if they are vaccinated?
3. If the ICSs increase the risk of pneumonia and exacerbation, is there any significant difference among ICSs?

It is suggested that vaccination has an important role in preventing exacerbations and pneumonia, which are the main problems in COPD. Previous studies showed that COPD patients with pneumonia had a greater need for intensive care unit (ICU) hospitalization, longer hospitalization time, and higher mortality rates compared to COPD patients without pneumonia (11,12). In these studies, the analysis of hospitalizations due to COPD exacerbation revealed that pneumonia accounts for 36% of the first hospitalizations due to COPD exacerbations. Therefore, pneumococcal vaccination is recommended for all adults in the risk group. In Spain, the PCV13 vaccination program for COPD patients above the age of 50 is considered a cost-effective strategy (7). The Community-Acquired Pneumonia Immunization Trial in Adults (CAPITA), a large, double-blind, randomized study, showed that PCV13 provides an effective immune response in preventing pneumonia and invasive pneumococcal disease in adults over 65 years of age (13). Jackson et al. reported that a decrease in pneumococcal infections was observed in adults with the addition of PCV13 to the pediatric vaccination calendar in 2010 (14). In a review conducted in 2017, Walters et al. reported that pneumococcal vaccination reduced the number of exacerbations and pneumonia episodes and improved the quality of life in patients with COPD (15). Similar to

previous studies, this study revealed that the number of exacerbations and pneumococcal pneumonia episodes decreased significantly after the administration of pneumococcal vaccine PCV13 in COPD patients.

Inhaled corticosteroids are commonly used agents, especially in asthma and COPD control. In previous studies, different conclusions have been reported about the effects of ICSs on acute exacerbation and pneumonia in patients with COPD. The use of ICS in COPD has been shown to be effective in reducing exacerbations and controlling the disease (16). Similarly, Lutter et al. reported that COPD patients treated with an ICS had improvement in quality of life and CO diffusing capacity (17). On the other hand, a four-year prospective randomized study suggested that ICS, especially fluticasone propionate, may adversely affect patients with frequent COPD exacerbations (18). Some previous studies showed that the use of ICS increases the risk of developing pneumonia in patients with COPD. These previous studies suggest that ICS can alter habitual flora and antimicrobial sensitivity, especially in COPD patients with chronic airway infections (19). In this study, there was a significant decrease in the mean number of exacerbations and pneumonia episodes in the post-vaccination period in patients using ICS, however, this significant decrease was not observed in patients not using ICS. Thus, we concluded that the use of ICS had no effect on the success of PCV13 in reducing the exacerbation and pneumonia in COPD patients. Nevertheless, the comparison of the mean exacerbation and pneumonia changes showed no difference between the patients using ICS and not using ICS. However, it should be noted that there was a significant gap in patient series between these two groups (patient series, 90 vs 18).

It is thought that the pneumonia or exacerbation risk potential of different ICS formulations may vary due to their different pharmacokinetics. In an epidemiological study in Canada, Suissa et al. reported a 101% higher risk of pneumonia in COPD patients treated with fluticasone propionate and a 17% higher risk of pneumonia in budesonide-treated patients compared to controls not treated with ICSs (20). In another study comparing budesonide and fluticasone propionate, a lower incidence of severe adverse pneumonia was reported in budesonide-treated patients (21). Similarly, Morjaria et al. showed that fluticasone propionate significantly increases the risk of pneumonia compared to other types of ICS. This was attributed to the different behaviour of flutica-

sone from other ICS such as beclomethasone and budesonide. Fluticasone drags electrons across the molecule, changing not only the strength but also the lipid solubility. In vivo, this is characterized by a change in the volume of distribution and a longer stay of fluticasone in lipid membranes. As a result, it was predicted that it would have significant effects on lung immunity and epithelial barrier function, and therefore inflammatory responses would decrease (17). Although some previous studies reported that ICSs such as fluticasone propionate and budesonide may increase the risk of pneumonia in COPD patients, this study revealed that acute exacerbation and pneumonia decreased in vaccinated COPD patients using ICSs, even significantly among those using fluticasone propionate. Also, no significant difference was found among the ICS type groups when the number of exacerbations and pneumonia, within one year before and after the vaccination date, was compared according to the inhaler steroid type. These findings of the present study were in concordance with the previous studies.

The learning points of this study were as follows:

1. Pneumococcal vaccination may reduce COPD exacerbation and pneumonia within one year.
2. According to the findings of this study, neither ICS use nor type of ICS appears to be possible co-factors for COPD exacerbation and pneumonia in vaccinated COPD patients.

The main limitation of this study is that it is a retrospective study. Therefore, patients' exacerbation and pneumonia stories have been evaluated through the drugs used and hospitalization records in the social security registry system. Another limitation is that the number of our patients not using any ICS is relatively small compared to patients using ICS.

CONCLUSION

In conclusion, PCV13 vaccination provides a significant decrease in both exacerbation and pneumonia frequency in COPD patients. It is important to develop strategies for the administration of the pneumococcal vaccine in COPD patients. Another significant outcome of this study is that the use of ICS and the type of ICS have no positive or negative effect on acute exacerbation and pneumonia episodes in vaccinated COPD patients. Further prospective-designed studies with larger patient series are required to substantiate these outcomes.

Ethical Committee Approval: To conduct this study, the necessary permission was taken from Health Sciences University Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital after the evaluation of Medical Specialization Education Board (TUEK) (Decision No: 8528, Date: 07.11.2018).

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: GK, GVŞ, GP, EY, MOG

Analysis/Interpretation: GVŞ, GP, FDÜ

Data acquisition: MOG, FDÜ, AA

Writing: GVŞ, MOG, GK, AA

Clinical Revision: GK, FDÜ, GP, AA, EY

Final Approval: EY

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