UTICAJ KOMORBIDITETA NA POJAVU EGZACERBACIJA MEĐU OBOLELIM OD HOBP USLED ZAPOSTAVLJENE IMUNIZACIJE PROTIV SEZONSKOG GRIPA

THE INFLUENZE OF COMORBIDITY ON ACUTE EXACERBATION AMONG COPD PATIENTS BECAUSE TO NEGLECT IMMUNIZATION AGAINST SEASONAL FLU

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Sažetak

Uvod: Smernice, Svetske zdravstvene organizacije (SZO), Centra za kontrolu bolesti SAD (CDC) i nacionalne, preporučuju imunizaciju protiv virusa gripe (nivo dokaza A, stepen preporuke 1) među pacijentima starijih od 65 godina i posebno među hroničarima. Egzacerbacije hronične opstruktivne bolesti pluća (HOBP) često nastaju usled infekcija virusima, najčešće virusi influence (gripa). Međutim, stepen imunizacije je i dalje niži od preporučenog kako kod nas, tako i u razvijenim zemljama.

Cilj rada je bio da se utvrdi učestalost i efektivnost imunizacije protiv sezonskog gripa u cilju prevencije egzacerbacija kod HOBP pacijenata sa komorbiditetima.

Metod: Sprovedena je prospektivna studija kod ambulantnih HOBP pacijenata u trogodišnjem periodu (2014 – 2017) u Polikliničkoj službi Instituta za plućne bolesti Vojvodine, Sremska Kamenica. Povezanost vakcinacije i HOBP egzacerbacija, kao i starosti i komorbiditeta ispitivana je u univarijantnoj i multivarijantnoj logističkoj regresionoj analizi.

Rezultati: Studija je obuhvatila 840 pacijenata (468 muškaraca); 37,1% pacijenta je vakcinisano protiv sezonskog gripa. Komorbiditete je imalo 741 pacijent, najčešće je bio povišen krvni pritisak (597, 71.1 %) i diabetes mellitus (180; 21.4%). Egzacerbacije HOBP su bile češće kod nevakcinisanih pacijenata (176 (31.9%) vs. 375 (68.2%), $p=0.043$). Stariji, vakcinisani pacijenti (≥ 65 godina), imali su manje egzacerbacija u odnosu na nevakcinisane (89 (56.0%) vs. 188 (69.4%), $p=0.005$). Manje egzacerbacija je potvrđeno u grupi vakcinisanih pacijenata sa komorbiditetima (165 (61.1%) vs. 327 (69.4%), $p=0.021$). U multivarijantnoj analizi su nezavisni prediktor pojave egzacerbacije je bila srčana slabost (RR 2.734; 95% CI (1.121 - 6.669); $p=0.027$).

Zaključak: Imunizacija protiv sezonskog gripa i dalje je ispod preporučenog nivoa. Vakcinacija protiv sezonskog gripa značajno redukuje egzacerbacije među HOBP pacijentima, posebno kod starijih i sa kardijalnim komorbiditetom.

Ključnereči: komorbiditet, vakcinacija, grip, HOBP, egzacerbacija

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a significant sociomedical issue for both the patient and the society. It is estimated that 11 – 12% of the world population suffers from COPD. The prevalence is significantly higher among smokers and elderly population.^{1,2} The more frequent the exacerbations, the quicker the progression of the disease, followed by decrease in the quality of life, increase in number of hospitalizations, severity and mortality.³ Viruses account for up to 50% COPD exacerbations and the influenza virus up to 28% of

seasonal viruses (winter months).⁴⁻⁷ The World Health Organization (WHO) and European Center for Disease Prevention and Control, (ECDC), US Centers for Disease Control and Prevention (CDC) as well as the National Guide for Good Clinical Practice for COPD of the Republic of Serbia (2013) recommend that patients with COPD undergo immunization for influenza (Evidence Level A, Recommendation Degree 1).^{8,9} Vaccination against influenza leads to a reduction in contraction of the virus by 60%, number of hospitalizations up to 40% and reduction in occurrence of pneumonia.¹⁰⁻¹² This is recommended for all patients over 65 and the chronically ill.¹³⁻¹⁴

The European Union (EU) aim is to vaccinate 70% of patients with chronic diseases. From 2012 – 2016, the number of those vaccinated averaged 45%; in the US around 40% in 2016.^{15,16} In Serbia, in the 2009-2010 season, after the A H1N1 flu pandemic, immunizations against seasonal flu were at 2%, the following years 35%, and last 2 years from 85-89 %.¹⁷ The bulk of financial support goes to acute exacerbation; 25% to hospitalizations, which last 10 days on average. In the US, COPD leads to the urgent care of 1.4 million cases and nearly 662,000 hospitalizations (1.9% of all hospitalizations).^{18,19}

The seasonal flu vaccination effects among COPD patients have been demonstrated in most of the studies coming from highly-developed countries as opposed to low or middle income countries where there has not been much research into this issue. Among these countries is Republic of Serbia, where there has been no research on the effects of this immunization and COPD and this continues to be a great burden because of great health budget outlays from society as well as the patients themselves. This study has arisen from the desire to show COPD patients and the medical community the need for continued education and advice about immunization against seasonal flu.

The main aim was to determine the frequency of flue vaccination in a cohort of COPD patient. Then, there was examined the effectiveness of the vaccination against seasonal flu among COPD patients, more specifically to determine if the vaccine reduced exacerbations among COPD patients. Also, the assessment of influence of patient related factors such as age, comorbidities and BMI in relation to vaccination status on reducing exacerbations in COPD patients.

MATERIALS AND METHODS

This prospective trial was conducted over a time period of three years and it included consecutively ambulatory patients with COPD (2014 – 2017), at the Polyclinic for Pulmonary Diseases, Institute for Pulmonary Diseases of Vojvodina (IPDV) in Sremska Kamenica, Serbia. The study was approved by the Ethical committee of the IPDV. We collected basic demographics data and medical histories of the patients with an established COPD diagnosis. The demographic data included gender, age, smoking

habits (packs per year) and body mass index. The criteria for being included in the study were: patient age over 40, with COPD diagnosis (based on a post-bronchodilator FEV1/FVC ratio of < 0.70)¹ of at least one year, stable phase of the diseases (non-systemic use of corticosteroid therapy within 6 weeks, prior the study). Patients who were suffering from cancer within the 5 years are excluded from the study. Vaccination status (immunization against seasonal flu) and comorbidity were obtained from the patient files and medical history at IPDV, but also as given by the patient. Vaccinations were performed by the patients' general practitioner doctor in their local health centers.

The study encompassed a once-per-year monitoring of each patient. We also collected the data on exacerbations one year prior to entering into the research from the patient files and medical history at IPDV. We analyzed moderate and severe exacerbations; moderate requires treatment with systemic corticosteroids or antibiotics; severe requires hospitalization or evaluation in the emergency department.²⁰

Descriptive statistics were generated for all study variables, including mean and standard deviation (SD) for continuous variables and relative frequencies for categorical variables. The chi-squared test was used to determine whether there is a significant difference between the expected frequencies and the observed frequencies in one or more categories. The predictive values of evaluated variables for COPD exacerbations were evaluated with univariate and multivariate logistic regression analysis. All probability values were calculated by assuming a 2-tailed α value of 0.05 with confidence intervals at the 95% level. All statistical analyses were performed with SPSS for Windows version 17 (SPSS Inc., Chicago, IL).

RESULTS

The study included 840 patients (468 males and 372 females). The average age was 65.39 ± 8.60 (youngest 43, oldest 90), average packs of cigarettes per year 45.67 ± 25.09 (796-94.7 % smokers and former smokers), and average length of COPD was 7.64 ± 5.44 years (min. 1 year, max. 31 years). Total of 312 (37.1%) were vaccinated against seasonal flu. There were 741 patients with comorbidity; the most frequent being arterial hypertension (n=597;

71.1%), diabetes mellitus (n=180; 21.4%), heart failure-NYHA $\geq$ 2 had 36 (4.3%) patients. One comorbidity was present in 290 patients (34.5%), two in 233 (27.7%) and three or more in 185 (22%). Concurrent presence of cardiovascular disease (CVD - arterial hypertension, arrhythmia, ischemic heart disease, heart failure), diabetes mellitus (DM) and depression were found in 20 patients (2.4%). Only 99 (11.8%) patients were without comorbidity. (Table 1) COPD exacerbations were present in 663 patients (78.9%) over the previous year (prior to entering the research). After one year of monitoring, 271 patients (32.3%) had no exacerbations. Exacerbations decreased in 551 patients (65.6%). (Table 1) Five patients passed away (0.6 %); 1 due to severe exacerbation with pneumonia, 3 at home, 1 in traffic accident. Exacerbations occurred more frequently in non-vaccinated compared to vaccinated patients (176 (31.8%) vs. 375 (68.1%), $p=0.043$), as well as pneumonia (6 (33.3%) vs. 12 (66.7%), $p=0.028$) (Table 2) 430 patients were older, ≥ 65 , (51.3%), there was no significant statistical difference of frequency of vaccinated patients between younger and older patients (159 (36.9%) vs. 271 (63.1%), ($p=0.92$). Significantly more exacerbations were noted in those older than 65, vaccinated persons in relation to the non-vaccinated (89 (56.0%) vs. 188 (69.4%), $p=0.005$). (Table 2) Lower frequency of exacerbations was confirmed in vaccinated patients with comorbidity in relation to non-vaccinated patients (165 (61.1%) vs. 327 (69.4%), $p=0.021$). (Table 2) There was no noted statistically significant difference in the frequency of exacerbations in patients without comorbidity in relation to those vaccinated (27 (64.3%) vs. 33 (57.9%), $p=0.520$). Vaccinated patients who suffer from heart failure (NYHA $\geq$ 2) had lower frequency of exacerbation in relation to non-vaccinated patients (6 (66.7%) vs. 24 (88.9%), $p=0.043$). (Table 2) There was no noted statistically significant difference in the frequency of exacerbations in patients without heart failure in relation to those vaccinated (186 (61.4%) vs. 336 (67.1%), $p=0.102$). There was no noted statistically significant difference in the frequency of exacerbations in patients who didn't suffer from concurrent CVD, DM and depression in relation to the vaccination status (192 (61.5%) vs. 340 (66.9%), $p=0.116$). There was not a single, vaccinated patient with a combination of these diseases (CVD, DM and

depression). (Table 2) In univariate analysis vaccination, COPD duration and heart failure were significant predictors of exacerbation, while age ≥ 65 and comorbidities were not (Table 2.). In multivariate analysis heart failure were independent predictors of exacerbations.

DISCUSSION

The results of the study demonstrated low vaccination rates as well as significant reduction in COPD exacerbations in vaccinated compared to non vaccinated patients during one year follow up. The reason for the lower percentage of vaccinated patients (312; 37.1%) can be explained by the distrust to the effectiveness to immunization against seasonal flu. This is, in part, a result of the media campaign against any type of vaccinations.^{21,22} Then, second reason is a fear of undesired post-vaccine reactions. According to data from the Agency for Medicines and Medical Devices (ALIMS), Republic of Serbia, in 2015 there was a lower number of registered undesired reactions (mainly skin reactions) after immunization than the previous year.²³ Broder reported, after the development of Swine Flu (2009), that there were no undesired events after vaccination.²⁴ Also important reason for rejection of immunization is the fear of getting the flu and exacerbation of COPD just after the vaccination. Zimmerman reported that 38 % non-vaccinated persons thought that they could get the flu after vaccination.²⁵ Ting researched the post-vaccination period and occurrences of exacerbation within 3 weeks after immunization.²⁶ That study confirmed that exacerbations which occurred immediately after the vaccine were not statistically significant, that is, that they did not contribute to the development of exacerbations of COPD after vaccination. The impact of health care workers is also important for non-immunization. Only 8.7% of the health staff in Serbia were vaccinated in the 2016-2017 season.¹⁷ Kopitovic demonstrated that many physicians did not accept that they suffered from COPD and were not vaccinated against seasonal flu.²⁷ Similar was in Zimmerman study, where almost one-third of non-vaccinated persons didn't get information from their doctors regarding vaccination.²⁵

Poole has shown (a Cochrane analysis) the results of 11 studies regarding the efficacy of the influenza vaccine and COPD.²⁸ There was a fall in the number of exacerbations, but because of the small number of patients there was no confirmation of relation to mortality. However the number of exacerbation of COPD fell among those who received the immunization. In univariate logistic regression analysis, vaccination was significant predictor of exacerbation ($p=0.048$). Nichol noted a lower number of ER visits in groups of vaccinated patients.²⁹ Garrastazu, with his 899 vaccinated patients, had fewer hospitalizations (severe exacerbations) over the year of monitoring.³⁰ Montserrat-Capdevila analyzed 1323 patients over a three-year period, and reported fewer hospitalizations among vaccinated patients.³¹

Our finding about a lower frequency of exacerbations among those older than 65 in relation to non-vaccinated status ($p=0.005$) was similar to a South Korean study which analyzed 828 patients (54.2 % vaccinated).³² Nichol noted that persons older than 65 outside the flu season are hospitalized for flu and pneumonia (55 of 1000) and during the season the number doubles.²⁹

Compared to our study the Montserrat-Capdevila study from 2014 demonstrated similar results in number and type of comorbidities, the most frequent was arterial hypertension (597, 71.1%) and every fifth had diabetes (180, 21.4%) in our study.³¹ It has been confirmed that vaccinated patients with comorbidity have lower frequency of exacerbations in relation to non-vaccinated patients ($p=0.021$), which has been previously reported by Sogaard confirmed.³³ Wang showed that mortality in stroke victims and diabetes, as chronic diseases, were reduced among vaccinated against seasonal flu.³⁴ Vardeny, in 2016, demonstrated that there was less worsening of heart failure in patients vaccinated against seasonal flu.³⁵ Our research demonstrated that independent predictor of exacerbations was heart failure (patients with NYHA ≥ 2) ($p=0.027$). There were 20 patients who had CVD, DM and depression, at the same time, and none had been vaccinated. In this sub-group everybody had exacerbation (one of them passed away from exacerbation and pneumonia in the hospital). The reason for low level of immunization, in this sub-group, could be a fear of new exacerbation. Also, the second reason could be the low level of

knowledge and attitude to the effect of immunization.

There were three important **limitations to this work**. First was no laboratory confirmation of vaccination against seasonal flu. Informations about immunization were obtained from the patient files and medical history at IPDV, but also as given by the patient. Second was varying criteria for hospitalization or observation in emergency room at health institutions. Third, there was small a number of vaccinated patients, even a three year period. However, to our knowledge this is a first longitudinal study investigating flu vaccination effects in COPD patients in the this region, west Balkan.

In **conclusion** we have shown that there is a clear reduction in number of exacerbations, however it was not shown in multivariable analyse. Multivariable analyse confirmed that heart failure (NYHA ≥ 2) was independent predictors of exacerbations. From the aforementioned, it arises that there is a great need for consistent information and education of both chronic patients as well as the entire population with emphasis on including medical staff at all levels of the health system.

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Table 1. Characteristics of the study population and comorbidity

Characteristic	Result
Comorbidity(N, %)	741 (88.2)
1 cmb*	290 (34.5)
2 cmb	233 (27.7)
≥3 cmb	185 (22.0)
Arterial hypertension	597 (71.1)
Hiperlipoproteinemia	255 (30.3)
Ischemic heart disease	198 (23.6)
Diabetes mellitus (DM)*	180 (21.4)
Arrhythmia	177 (21)
Depression	52 (6.2)
Heart failure (NYHA≥2)*	36 (4.3)

Notes: Values expressed as n (%) or mean±SD,
Abbreviations: COPD, chronic obstructive pulmonary disease; BMI, body mass index; DM, diabetes mellitus; CVD, cardiovascular disease; NYHA, New York Heart Association; CMB, comorbidity

Table 2. Patient characteristics and vaccination status with univariate and multivariate analysis

Variable	Vaccination		p
	Yes 312 (37.1)	No 528 (62.9)	
Exacerbation-moderate and severe (N patients=551)	176 (31.9)	375 (68.1)	0.043
Age ≥65	89 (56.0)	188 (69.4)	0.005
CMB	165 (61.1)	327 (69.4%)	0.021
Without CMB	27 (64.3%)	33 (57.9%)	0.520
Heart failure (NYHA≥2)	6 (66.7)	24 (88.9%)	0.043
Without heart failure	186 (61.4%)	336 (67.1%)	0.102
Without CVD+DM+Depression	192 (61.5%)	340 (66.9%)	0.116
Univariate analysis	RR	95% CI	
age ≥65	0.889	0.668 - 1.182	0.418
CMB	1.284	0.835 - 1.976	0.255
vaccination	0.747	0.557 - 0.898	0.048
COPD duration	1.032	1.004 - 1.061	0.025
heart failure	2.701	1.111 - 6.567	0.028
multivariate analysis			
heart failure	2.734	1.121 - 6.669	0.027

Notes: Values expressed as n (%) or mean±SD,
Abbreviations: CMB, comorbidity; NYHA, New York Heart Association; CVD, cardiovascular disease; DM, diabetes mellitus; BMI, body mass index, COPD, chronic obstructive pulmonary disease.

Abstract

Introduction: Many guidelines (WHO, CDC, national) recommend immunization against influenza virus (Evidence level A, Level of recommendation 1) among elderly population (>65) and chronically ill.

The influenza virus is often a cause of exacerbations among chronic obstructive pulmonary disease (COPD) patients. But, vaccination rates are still below recommended even in developed countries.

The aim of the study was to examine the rates and effectiveness of immunization against seasonal influenza in prevention of exacerbations among chronic obstructive pulmonary disease (COPD) patients in Serbia.

Method: The prospective trial of stable chronic obstructive pulmonary disease outpatients conducted over three years (between 2014 - 2017) at Polyclinic department of Institute for pulmonary diseases of Vojvodina, Sremska Kamenica, Serbia. The rates and effects of seasonal flu vaccination on chronic obstructive pulmonary disease exacerbation rates were evaluated using univariate and multivariate logistic regression analysis, taking into account comorbidity, age.

Results: The study included 840 patients (468 males). The flu vaccination rate was 37.1%. There were 741 patients with comorbidity; the most frequent being arterial hypertension (n=597; 71.1%) and diabetes mellitus (n=180; 21.4%). Exacerbations occurred more frequently in non-vaccinated patients (176 (31.9%) vs. 375 (68.2%), $p=0.043$). Older vaccinated patients (≥ 65 years), had fewer exacerbations compared to non-vaccinated (89 (56.0%) vs. 188 (69.4%), $p=0.005$). Lower frequency of exacerbations was also confirmed in vaccinated patients with comorbidities (165 (61.1%) vs. 327 (69.4%), $p=0.021$). Multivariate analysis identified heart failure (RR 2.734; 95% CI (1.121 - 6.669); $p=0.027$) as independent predictors of COPD exacerbations.

Conclusion: Immunization for seasonal influenza in Serbia is below recommended rates. Flu vaccination was associated with significant reduction in chronic obstructive pulmonary disease patients exacerbation rates, particularly in elderly patients and patients with heart failure.

Keywords: comorbidity, vaccination, seasonal flu, COPD, exacerbation

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