



USE OF INHALED CORTICOIDS AS A RISK FACTOR FOR COMMUNITY-ACQUIRED PNEUMONIA IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

CORTICOIDES INHALADOS COMO FACTOR DE RIESGO DE NEUMONÍA ADQUIRIDA EN LA COMUNIDAD EN ENFERMEDAD PULMONAR OBSTRUCTIVA CRÓNICA

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ABSTRACT

Objective: To determine if the use of inhaled corticosteroids is a risk factor for community-acquired pneumonia in patients with Chronic Obstructive Pulmonary Disease at the Víctor Lazarte Echegaray Hospital during the period 2017-2020. **Methods:** The study was analytical, observational, retrospective of cases and unmatched controls in a ratio of 4:1, with a population of 405 subjects from whom 81 cases and 324 controls were selected, who met the selection criteria. A non-probabilistic sampling was carried out. The variables, use of inhaled corticosteroids, patients with community-acquired pneumonia, age, sex, malnutrition and smoking were included. The association was measured using Pearson's non-parametric Chi-square test and Fisher's exact test at lower frequencies less than 5. The bivariate and multivariate analysis was performed using multiple logistic regression with statistical significance (p value <0.05). The study statistician was the odds ratio (OR). **Results:** Through the multivariate analysis of the variables under study, no relationship was found between the use of inhaled corticosteroids and patients with community-acquired pneumonia (OR= 1.17; 95%CI: 0.48-2.99 and p value=0.737). It was observed that only age can be considered as a risk factor in view of its significance (OR=1.09; 95%CI: 1.06-1.12 and p value<0.001), while the variables sex, malnutrition, and smoking proved not to be significant (p > 0.05). **Conclusions:** The use of inhaled corticosteroids is not a risk factor for community-acquired pneumonia in patients with chronic obstructive pulmonary disease.

Keywords: Chronic obstructive pulmonary disease (COPD), Corticosteroids, Pneumonia. (Source: MESH-NLM)

RESUMEN

Objetivo: Determinar si el uso de corticoides inhalados es factor de riesgo de neumonía adquirida en la comunidad en pacientes con enfermedad pulmonar obstructiva crónica en el Hospital Víctor Lazarte Echegaray durante el período 2017-2020. **Métodos:** El estudio fue analítico, observacional, retrospectivo de casos y controles no emparejados a razón de 4:1, con una población de 405 sujetos; se seleccionaron 81 casos y 324 controles, quienes cumplieron los criterios de selección. Se realizó un muestro no probabilístico. Se incluyeron las variables, uso de corticoides inhalados, pacientes con neumonía adquirida en la comunidad, edad, sexo, desnutrición y tabaquismo. La medida de asociación se hizo utilizando la prueba paramétrica Chi Cuadrado de Pearson y la prueba exacta de Fisher en frecuencias menores de 5. El análisis bivariado y multivariado se realizó mediante regresión logística múltiple con significancia estadística (valor p <0,05), El estadígrafo de estudio fue el odds ratio (OR). **Resultados:** Mediante el análisis multivariado de las variables en estudio, no se encontró relación entre el uso de corticoides inhalados y pacientes con neumonía adquirida en la comunidad (OR= 1,17; IC 95%: 0,48-2,99 y valor de p=0,737). Se observó que solo la edad puede considerarse como factor de riesgo en vista de su significancia (OR=1,09; IC 95%: 1,06-1,12 y valor de p<0,001), mientras que las variables sexo, desnutrición y tabaquismo demostraron no ser significativos (p > 0,05). **Conclusiones:** El uso de corticoides inhalados no es factor de riesgo de neumonía adquirida en la comunidad en pacientes con enfermedad pulmonar obstructiva crónica.

Palabras clave: Enfermedad pulmonar obstructiva crónica (EPOC), Corticoides, Neumonía. (Fuente: DeCS- BIREME)

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is defined as a common, preventable, and treatable disease characterized by respiratory symptoms and a persistent and irreversible reduction in airflow caused by alveolar abnormalities after exposure to harmful particles or substances⁽¹⁾. In 2016, the estimated prevalence of this disease was 251 million cases. In 2015, approximately 3.17 million people worldwide died from COPD, accounting for an alarming 5% of all deaths recorded that year⁽²⁾.

Currently, pharmacological treatment of COPD is the cornerstone for achieving an adequate lung function and a potential reduction of exacerbations, which is based on the combination of inhaled corticosteroids and beta-adrenergic agonists^(3,4). It is the former that can lead to the occurrence of several adverse effects, albeit to a lesser extent than oral corticosteroids⁽⁵⁾. In other words, the use of inhaled corticosteroids has been associated with an increased likelihood of developing infectious processes, with community-acquired pneumonia (CAP) being the most common and well-documented. The risk of this is further elevated by patient-specific characteristics such as advanced age and comorbidities⁽⁶⁾.

Therefore, it is important to understand the risk-benefit profile of using these medications before recommending and/or initiating therapy with them⁽⁷⁾. Previous studies have demonstrated an association between the use of inhaled corticosteroids and CAP in patients with COPD^(8,9,10,11). Therefore, the aim of this article is to determine if the use of inhaled corticosteroids is a risk factor for community-acquired pneumonia in patients with Chronic Obstructive Pulmonary Disease at the Hospital Víctor Lazarte Echegaray during the period 2017-2020, with the expectation of finding a relationship between the two variables.

METHODS

Design

An analytical, observational, retrospective case-control study was conducted, unmatched, with a 1:4 ratio of cases to controls. The present study was carried out at the Hospital Víctor Lazarte Echegaray in 2021, where data were collected from the medical records of patients treated between 2017 and 2020.

The target population consisted of patients diagnosed with COPD and treated at the Hospital Víctor Lazarte Echegaray during the period 2017-2020, where cases were defined as patients with CAP, and controls were defined as patients without CAP.

Procedures and variables

The inclusion criteria for cases and controls included a diagnosis of COPD, age over 45 years, both sexes, and medical records containing the variables under study. Exclusion criteria included nosocomial pneumonia, asthma, exacerbations in the last six months, antibiotic use in the last three months, immunosuppressive therapies, and lung cancer.

The independent variable in the study was the use of inhaled corticosteroids, specifically Beclomethasone or Fluticasone, which were considered as pharmacological therapy for COPD. The dependent variable was the diagnosis of CAP, defined as a respiratory clinical picture with signs of pulmonary consolidation and confirmed radiological findings, documented in the medical records. Other variables such as age, sex, malnutrition, and smoking were recorded, which were obtained from the anamnesis and medical history described in the medical records. All the aforementioned data were recorded on a data collection form for each study subject, which was stored for subsequent analysis and statistical evaluation.

Population and Sample

For the calculation of the sample size, a confidence interval of 95%, statistical power of 80%, and a ratio of 1 case to 4 controls were considered. The results obtained by Wang et al.⁽¹²⁾ were used, with a proportion of exposed cases of 50.5%, proportion of exposed controls of 30.3%, and an odds ratio of 2.025. The open-access epidemiological package Epidat 4.2 was used for the sample calculation, resulting in a total of 405 patients, including 81 cases and 324 controls. A non-probabilistic sampling method was used.

Ethical Considerations

Authorization was obtained from the Ethics Committee of Hospital Víctor Lazarte Echegaray. As it was an observational study where the variables were not manipulated, informed consent was not applied.



Instead, the principle of confidentiality, as detailed in the Helsinki Declaration II (Sections: 11, 12, 14, 15, 22, and 23), was taken into account⁽¹³⁾.

Statistical Analysis

Data collection forms were transferred to an Excel® 2013 spreadsheet, and the obtained information was analyzed using IBM SPSS Statistics 26. The corresponding expense was covered to access the license for this specialized service. Results were presented using means and standard deviations for quantitative variables, or medians and interquartile ranges (IQR). For qualitative variables, frequencies and percentages (cross-tabulations) were used. To determine the association between the use of inhaled corticosteroids and CAP in patients with COPD, both

bivariate and multivariate analyses (multiple logistic regression) were used, with odds ratio as the measure of risk, along with the respective 95% confidence interval. Pearson's chi-square test was used for association. Given the nature of the design, odds ratio (OR) was used. Fisher's exact test was applied for frequencies less than 5, only calculated for a 2x2 table.

RESULTS

Out of the total sample of 405 patients with COPD, there was no missing information in the medical records. Among them, 81 patients had CAP, while 324 patients did not. The percentage of inhaled corticosteroid use was higher in patients with CAP (91.4%) compared to those without CAP (88.3%). However, no statistical significance was found between these groups, with a p-value of 0.429. (Table 1)

Table 1. Univariate analysis

Use of inhaled corticosteroids	Neumonía adquirida en la comunidad				χ^2 Test
	N.º	Yes	%	No	
Yes	74	91.4	286	88.3	$\chi^2 = 0.62$
No	7	8.6	38	11.7	p= 0.429
Total	81	100	324	100	

p-value obtained from the non-parametric Chi-square test (χ^2)

The mean and standard deviation of age for both groups were 76.1 ± 9.6 and 65.6 ± 11.5 , respectively, showing a significant difference in the mean age between the two groups, as well as statistical significance with a $p < 0.001$. The percentage of male gender was higher in patients with CAP (59.3%) compared to those without CAP (54.3%), but there was no statistically significant difference between the groups with a p-value of 0.424. The percentage of

malnutrition in patients with CAP was 8.6%, higher than in patients without CAP (3.4%), with a p-value of 0.040, demonstrating a statistically significant difference through the chi-square test. However, when the Fisher's exact test was applied, a p-value of 0.055 was obtained. The percentage of smoking in patients with CAP was 4.9%, lower than in patients without CAP (7.1%), and there was no statistically significant difference between the two groups with a p-value of 0.486. (Table 2)

Table 2. Bivariate logistic regression analysis.

Risk factor		Community-Acquired Pneumonia				χ^2 Test	Fisher's Exact Test
		Yes		No			
		N.º	%	N.º	%		
Use of inhaled corticosteroids	Yes	74	91.4	286	88.3	$\chi^2=0.62$ p=0.429	-
	No	7	8.6	38	11.7		
Age \geq 60 years	Yes	76	93.8	215	66.4	$\chi^2=24.1$ p<0.001	-
	No	5	6.2	109	33.6		
	Mean \pm SD	76.1 \pm 9.6		65.6 \pm 11.5			
Male gender	Yes	48	59.3	176	54.3	$\chi^2=0.64$ p=0.424	-
	No	33	40.7	148	45.7		
Malnutrition	Yes	7	8.6	10	3.4	-	0.055*
	No	74	91.4	314	96.6		
Smoking	Yes	4	4.9	23	7.1	$\chi^2=0.49$ p=0.486	-
	No	77	95.1	301	92.9		
Total		81	100	324	100		

P-value obtained from the non-parametric Chi-square test (χ^2)

* Expected frequency less than 5

A logistic regression model (multivariable analysis) was performed to adjust the Odds ratio of inhaled corticosteroid use for variables that have a demonstrated effect on CAP. In the simultaneous evaluation, the use of inhaled corticosteroids showed an Odds ratio of 1.17 (p=0.737, 95% CI: 0.48-2.99), age

had an Odds ratio of 1.09 (p<0.001, 95% CI: 1.06-1.12), male gender had an Odds ratio of 1.45 (p=0.169, 95% CI: 0.85-2.53), malnutrition had an Odds ratio of 1.18 (p=0.768, 95% CI: 0.39-3.57), and smoking had an Odds ratio of 2.10 (p=0.228, 95% CI: 0.63-7.06). Among these variables, only age showed statistical significance.

Table 3. Analysis with multiple logistic regression.

Factor	Coefficient β	Wald	Significance	OR	OR Interval	
					Lower limit.	Upper limit.
Use of inhaled corticosteroids	0.160	0.112	p = 0.737	1.17	0.48	2.99
Age	0.087	40.378	p < 0.001	1.09	1.06	1.12
Male gender	0.382	1.889	p = 0.169	1.45	0.85	2.53
Malnutrition	0.166	0.087	p = 0.768	1.18	0.39	3.57
Smoking	0.745	1.454	p = 0.228	2.10	0.63	7.06
Constant	-8.629	35.374	p < 0.001			
Model efficiency			79.5%			



DISCUSSION

This case-control study, conducted on a population of 405 patients with COPD at Hospital Víctor Lazarte Echegaray between 2017 and 2020, aimed to identify whether the use of inhaled corticosteroids and other associated factors constitute a risk for the development of CAP. In the multivariate analysis (Table 3), it is described that the use of inhaled corticosteroids is not significantly associated with the diagnosis of CAP. Therefore, it is assumed that their use is not a risk factor.

This finding is consistent with the study by Almagro P et al. in Spain in 2019⁽¹⁴⁾, which states that the conclusion that pneumonia cases increase in COPD patients treated with inhaled corticosteroids is not fully supported by data and cannot be considered confirmed. Supporting this stance, they argue that the incidence of pneumonia is not homogeneous in different studies and randomized clinical trials conducted over the years, suggesting that other factors such as the specific drug, dose, and different characteristics of the study population, including the misdiagnosis of pneumonia itself, may affect this risk. Contradictory findings were reported in the TORCH study (Towards a Revolution in COPD Health) by Crim C et al. in 2009⁽¹⁵⁾, which first reported the risk of pneumonia due to the use of inhaled corticosteroids. The authors found a relative risk of pneumonia of 1.52 (1.32-1.76), as well as an incidence rate of pneumonia per 100,000 people: 5200 for non-users of inhaled corticosteroids and 8800 for users.

This finding is also consistent with the study by Lee JH et al. in Korea in 2020⁽¹⁶⁾, where pneumonia was diagnosed more frequently in users of inhaled corticosteroids compared to non-users (33.7% vs. 24.5%, $p < 0.001$), with an incidence rate per 100,000 people: 8904 for users of inhaled corticosteroids and 6206 for non-users. Similarly, Cheng H et al. conducted a meta-analysis in 2021⁽¹⁷⁾, analyzing 59 randomized clinical trials, including recent studies, which revealed that all types of inhaled corticosteroids increase the risk of pneumonia in COPD patients, with a dose-response

relationship confirming the causality between the two variables in question.

In our study, the only independent factor significantly associated with acquiring CAP in COPD patients is age, affirming that the risk of CAP increases by 9% with each year of age, with a mean age of 76.1 years. Similar findings were reported by Mullerova et al. in the UK in 2012⁽¹⁸⁾ and Crim C et al. in 2015⁽¹⁹⁾, indicating in both studies that COPD patients over the age of 65 are significantly associated with a higher risk of CAP. However, Sheng Hao Lin et al. in 2016⁽²⁰⁾ concluded that both age greater/equal to 55 years and a reduced BMI ($< 25 \text{ kg/m}^2$) are considered independent risk factors for developing CAP in COPD patients. They based this on the reasoning that older individuals have a deteriorated functional state and those with a decreased BMI may have a strong association with the immune response. However, in the multivariate analysis, malnutrition (BMI $< 18.5 \text{ kg/m}^2$) did not show a significant association, so malnutrition cannot be considered a risk factor for CAP in COPD patients.

On the other hand, no significant difference was observed between males and females. In other words, both male and female COPD patients have similar risks of developing CAP. Jain NK et al. in India in 2011⁽²¹⁾ state that gender differences vary in terms of clinical presentation, radiological expression of COPD, and comorbidities each gender presents, which suggests that there is no difference between the sexes in the presentation of complications. They even refer to a sociocultural factor that often goes unnoticed, stating that the prevailing notion that COPD mainly affects men may put women at particular risk of underdiagnosis.

Regarding smoking, it could not be demonstrated as a risk factor for CAP in COPD patients. Dionne CW et al. in 2017 in the UK⁽²²⁾ also found no differences in the risk of CAP between non-smokers and current smokers, indicating that smoking does not have an additional impact on the risk of pneumonia in COPD patients. Furthermore, the study refers to the existing pathophysiological differences among COPD subgroups that could contribute to the observed differences in the risk of CAP.

Although there are theoretical mechanisms related to the increased risk of pneumonia due to smoking, such as physiological and structural changes caused by smoking, increased bacterial virulence, and smoking-induced dysregulation of immune function, further research is needed to establish smoking as a risk factor.

In conclusion, our study has limitations. While it provides some clarity regarding the relationship between the variables under investigation, being a retrospective case-control study does not establish an absolute reality. This warrants the need for more complex studies. Additionally, the information

obtained from the patients' medical records was used, and it is important to note that the veracity of the data could not be verified; therefore, it was assumed to be true. In other words, there is a possibility of information bias.

CONCLUSION

It is concluded that the use of inhaled corticosteroids is not a risk factor for CAP in patients with COPD. It is recommended to promote further research studies in order to obtain a more representative sample and keep the information updated based on our current reality.

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