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Inhaled corticosteroids and incidence of pneumonia in chronic obstructive pulmonary disease (COPD) patients: A review

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a worldwide respiratory disease that causes significant morbidity and mortality. The primary emphasis in managing COPD is on symptom control and preventing exacerbations. However, there has been ongoing discussion surrounding the safety of inhaled corticosteroids (ICS). This narrative review aimed to examine ICS influence on pneumonia in patients with COPD by consolidating findings from randomized controlled trials and observational studies. The data indicated that the utilization of ICS may be linked to a heightened susceptibility to pneumonia, with varying levels of risk reported across different ICS drugs. Regimens containing fluticasone were found to exhibit an increased susceptibility to pneumonia. The presence of a dose-dependent correlation between ICS and the incidence of pneumonia is apparent. Further investigation is necessary to clarify the fundamental principles and enhance treatment recommendations to maximize the management of COPD while minimizing the incidences of pneumonia associated with ICS.

ABSTRAK

Penyakit paru obstruktif kronik (PPOK) adalah penyakit pernapasan di seluruh dunia yang menyebabkan morbiditas dan mortalitas yang signifikan. Penekanan utama dalam penanganan PPOK adalah pada pengendalian gejala dan pencegahan eksaserbasi. Namun, ada diskusi yang sedang berlangsung seputar keamanan kortikosteroid inhalasi. Tinjauan naratif ini bertujuan untuk memeriksa pengaruh ICS terhadap terjadinya pneumonia pada pasien PPOK dengan menghimpun temuan dari uji coba terkontrol secara acak dan studi observasional. Data menunjukkan bahwa penggunaan ICS mungkin terkait dengan peningkatan kerentanan terhadap pneumonia, dengan berbagai tingkat risiko yang dilaporkan di berbagai obat ICS. Regimen yang mengandung flutikason telah ditemukan menunjukkan peningkatan kerentanan terhadap pneumonia. Adanya korelasi yang bergantung pada dosis antara ICS dan kejadian pneumonia terlihat jelas. Investigasi lebih lanjut diperlukan untuk mengklarifikasi prinsip-prinsip dasar dan meningkatkan rekomendasi pengobatan untuk memaksimalkan pengelolaan PPOK sambil meminimalkan insiden pneumonia yang terkait dengan ICS.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a manageable and curable respiratory illness that is a leading source of morbidity and mortality around the world. The condition can be identified through persisting bronchial restriction and respiratory symptoms, including dyspnea, persistent coughing, and secretion of sputum.[1] Over 3 million people died from COPD in 2022, and the disease's worldwide burden is predicted to rise in the following decades.[2]

Inhaled corticosteroids (ICS), long-acting agonist beta (LABA), and long-

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acting muscarinic antagonists (LAMA) have been used to prevent COPD exacerbations, regulate problems, and enhance rates of survival. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy, based on current data, maintains ICS use as an element of the primary therapy in COPD category D.[1] In COPD, the principal beneficial effect of ICS is a fifteen percent decrease in exacerbations in recurrent or heavy exacerbators.[3] Combination therapy of LABAs and ICS may interact positively compared to control or ICS only, potentiating local anti-inflammatory activities and decreasing exacerbations and mortality.[4]

Nevertheless, concerns about the safety of ICS persist as a significant issue. Inhalated corticosteroids are pharmacological agents with potent anti-inflammatory effects, but their mechanism of action is not specific to a particular target. As reported by several studies, ICS has been linked to various adverse effects, including upper respiratory tract infections, pneumonia, and candidiasis.[5] Pneumonia is a significant contributor to acute exacerbations in COPD.[6] Previous study has clearly shown a link between the use of ICS and an incidence of pneumonia. One study showed that the use of ICS/LABA in COPD patients was associated with a higher risk of pneumonia than LAMA monotherapy ($p = 0.0026$).[7] Nevertheless, other research has indicated that inhaled corticosteroids (ICS) do not substantially elevate the likelihood of contracting pneumonia.[8]

Understanding the specific pathways via which ICS enhances vulnerability to pneumonia still needs to be improved. However, there is a hypothesis suggesting that the immunosuppressive effects of ICS on the epithelium of the lungs and their ability to disturb the lung microbiota. There is a possibility that it may have an impact on the initiation and advancement of pneumonia.[9]

This review aimed to evaluate the evidence on the effect of ICS therapy on the incidence of pneumonia in COPD patients.

MATERIAL AND METHODS

Data sources

A narrative review was employed in our study, aiming to explore the effects of ICS use on the incidence of pneumonia in patients with COPD compared to non-ICS use. We performed electronic searches in Scopus and PubMed to identify full-text review articles with specific keywords such as “Inhaled Corticosteroids, ICS/LABA, Fluticasone/Salmeterol, Budesonide/Formoterol, Fluticasone/Vilanterol, Pneumonia, COPD”.

Eligibility

The prerequisites for inclusion in this narrative review were explicitly defined as follows: (1) randomized controlled trials with a minimal follow-up of six months and an IV trial phase in people with COPD or observational studies involving follow-up for a period of hospital stay (2) Using any ICS drug alone or in combination (ICS/LABA) with another medication as an intervention vs. a control group that did not use ICS (such as LABA, LAMA, or placebo), (3) diagnosis of incident pneumonia, (4) Original research-based papers from open-access journals, (5) literature that was written using the English language, (6) literature published in the last ten years. The duration of ICS exposure was not limited.

Data extraction

The data extraction process involved identifying and collecting relevant material that satisfied the predetermined criteria for inclusion (FIGURE 1).

RESULTS

All the main articles discussed the effect of ICS therapy on the cause incidence of pneumonia and had different results. The outcome of each study is presented in TABLE 1.

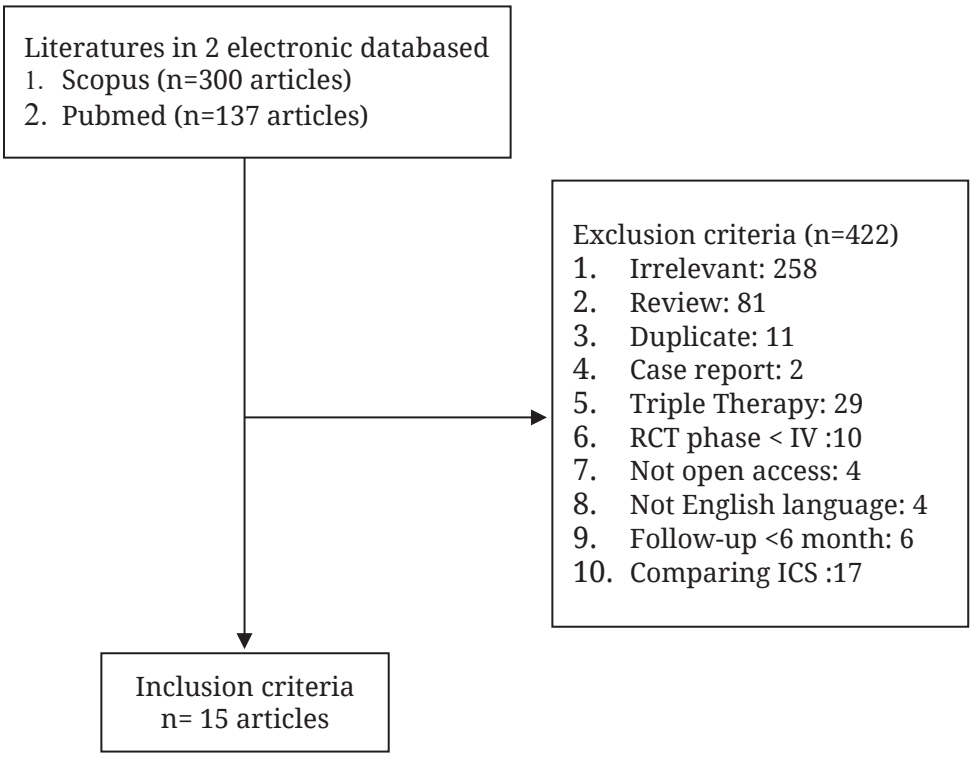

FIGURE 1. Study flowchart

TABLE 1. The result of ICS causes an incidence of pneumonia

Source	Method	Duration	Participants	Intervention	Result
Martinez *et al.*[10]	RCT	6 mo	1,909	• Fluticasone furoate/ vilanterol 200/25 µg (ICS/LABA); • Vilanterol 25 µg (LABA).	The ICS/LABA group had a higher risk of pneumonia than LABA alone (2 vs <1%).
Ohar *et al.*[11]	RCT	6 mo	734	• Fluticasone/salmeterol 250/50 µg (ICS/LABA); • Salmeterol (LABA)	The ICS/LABA group had a higher risk of pneumonia than LABA alone (4 vs 3%).
Rossi *et al.*[12]	RCT	6 mo	1,038	• Fluticasone/salmeterol 500/50 µg (ICS/LABA); • Indacaterol (LABA).	The ICS/LABA group had a higher risk of pneumonia than LABA alone (2 vs 0%).
Wedzicha *et al.*[13]	RCT	12 mo	5,328	• Fluticasone/salmeterol 500/50 µg (ICS/LABA); • Indacaterol/ glycopyrronium 110/50 µg (LABA/LAMA).	The ICS/LABA group had a higher risk of pneumonia than the LABA/LAMA group (4.8 vs 3.2%).
Wedzicha *et al.*[14]	RCT	12 mo	774	• Fluticasone/salmeterol 500/50 µg (ICS/LABA); • Indacaterol/ glycopyrronium 110/50 µg (LABA/LAMA).	The ICS/LABA group had a higher risk of pneumonia than the LABA/LAMA group (7.7 vs 3.6%).
Tashkin *et al.*[15]	RCT	4 yr	5,993	• ICS use (Fluticasone propionate group); • No-ICS use.	The ICS group had a higher risk of pneumonia than those without ICS (7.9 vs 5.9%).

TABLE 1. Cont...

Source	Method	Duration	Participants	Intervention	Result
Yawn *et al.*[16]	Cohort study	2 yr	1,669,546	• ICS user; • No-ICS user.	The ICS group had a higher risk of pneumonia than those without ICS (54 vs 0%).
Di Santostefano *et al.*[17]	Cohort study	6 mo	55,589	• ICS-containing medication; • LABD (LABA or LAMA).	The ICS group had a higher risk of pneumonia than those without ICS (4.87 vs 3.09%).
Morjaria *et al.*[18]	Cohort study	4 yr	3,700	• ICS; • No-ICS use.	The ICS group had a higher risk of pneumonia than those without ICS (6.8 vs 5.6%).
JH Lee *et al.*[19]	Cohort study	13 yr	87,594	• ICS users; • Non-ICS users.	The ICS group had a higher risk of pneumonia than those without ICS (33.73 vs 24.51%).
EG Lee *et al.*[20,21]	Cohort study	10 yr	4,699	• ICS/LABA; • LAMA.	The ICS/LABA group had a higher risk of pneumonia than the LAMA group (13.2 vs. 9.3%).
Wang *et al.*[22]	Case-control	12 yr	673,676	• ICS user; • No-ICS user.	The ICS group had a higher risk of pneumonia than those without ICS (50.5 vs. 49.5%).
Cascini *et al.*[23]	Nested-case-control	5 yr	29,150	• ICS; • No-ICS.	The ICS group had a higher risk of pneumonia than those without ICS (47.2 vs. 32%).
Hirano *et al.*[24]	Nested-case-control	4 yr	252	• ICS-treated patients; • ICS-untreated patients; • Non-ICS user.	The ICS group had a lower risk of pneumonia than those without ICS (5.16 vs. 9.82%).

DISCUSSION

Based on existing RCTs, this research showed that ICS is linked with an incidence COPD during respective clinical studies, although not statistically significant. The six randomized controlled trials documenting an elevated pneumonia risk have compared fluticasone alone (or in combination) and either placebo or alternative inhaled medicines. These trials have consistently seen a higher occurrence of pneumonia in the treatment groups that included fluticasone, whether administered alone or with other medications. In total, 924 participants completed the study, and there were more pneumonia recorded as adverse events (non-fatal) in the ICS-containing regimen (2%) than in the non-ICS-containing regimen (1%).[10] In other RCTs, observed pneumonia incidence in individuals treated with salmeterol/fluticasone (4%) and those treated with salmeterol alone (3%) are consistent with the findings reported in previous trials that have used salmeterol/fluticasone.[11,12] According to an additional investigation, the incidence of pneumonia was found to be 4.8% in the group treated with salmeterol-fluticasone. In comparison, it was 3.2% in the group treated with indacaterol-glycopyrronium (p=0.02).[13] Compared to the indacaterol/glycopyrone, the salmeterol/fluticasone exhibited a higher incidence of pneumonia (7.7 vs. 3.6%; p=0.046). These study findings suggest a potential link between the use of ICS therapy and an elevated vulnerability to pneumonia among patients with COPD. It's worth noting, however, that this observed difference did not reach statistical significance.[14] The incidence of hospitalized pneumonia was similarly elevated in long-term FP users compared to non-users. The percentage of persistent FP users hospitalized due to pneumonia

episodes (7.9%) was statistically higher than those without ICS treatment (5.9%).[15]

Observational studies show similar results to RCTs, but there are significant differences. This review included nine observational research, five cohort studies, three nested-case control studies, and one cross-sectional study. According to the research, the incidence of pneumonia in the ICS arms were 54% greater than in the non-ICS arms. The multivariate Cox regression analysis results revealed a dose-dependent relation between ICS and pneumonia risk.[16] The use of ICS-containing medications was related to an elevated incidence of pneumonia compared to LABA in a population-based COPD cohort (HR = 1.49; 95% confidence interval [CI]=1.22 - 1.83). The study looked at pneumonia rates (per 1000 person-years) for the ICS-containing and the LABD cohorts that had not been changed. The occurrences of the corresponding variables were 48.7 and 30.9.[17] During the study period, 7,473 (33.73%) ICS users received a diagnosis of pneumonia, which was more significantthan the 5,432 (24.51%) non-ICS users (p=0.0001). The occurrence frequency per 100,000 person-years had been 8904.98 for individuals using ICS, while 6206.79 for individuals not using ICS. A positive correlation was observed between the cumulative ICS dose and pneumonia. The occurrence of pneumonia shows variability based on the specific type, was as follows: 9,434.95 for fluticasone propionate, 7,614.98 for budesonide, 8,388.57 for beclomethasone, 7,252.61 for ciclesonide, and 12,278.90 for fluticasone furoate.[18,19] The group of patients who were administered ICS/LABA medication exhibited a greater occurrence rate of pneumonia compared to those who received LAMA treatment (93.96 vs. 136.42/1000 person-years; p= 0.0004). The HR is 1.374, and a 95%CI ranges from 1.116 to 1.692. Furthermore, the calculated p-value of 0.0028 indicates a statistically significant elevation in the probability of pneumonia within the ICS/LABA group compared to the LAMA group.[20]

The study discovered that taking ICS was associated with a 1.26 time increased incidence of pneumonia (OR= 1.26; 95% C =1.21 - 1.32). The occurrence of pneumonia in COPD patients exhibits variability based on the specific types of ICSs used. The data revealed a positive correlation between fluticasone/salmeterol, fluticasone, or a combination of fluticasone/salmeterol and fluticasone and the probability of pneumonia occurrence. The odds proportions (OR) and their related confidence intervals of 95%CI were observed as follows: 1.35 (95%CI=1.28–1.41) for fluticasone/salmeterol, 1.22 (95%CI =1.10–1.35) for fluticasone, and 1.33 (95%CI=1.27–1.39) for either fluticasone/salmeterol or fluticasone. In contrast, no statistically significant differences were found in the occurrence of pneumonia across individuals who used budesonide/formoterol (OR=1.02; 95%CI=0.96–1.08), budesonide (OR=1.06; 95%CI=0.99–1.13), or neither budesonide/formoterol nor budesonide (OR=1.03; 95%CI=0.99–1.08).[21]

The occurrence of pneumonia was found to be significantly elevated among individuals using ICS compared to those who did not use ICS (35.3 vs 7.5%: p<0.05). The findings from the multivariate analysis revealed a substantial and independent correlation between acute exacerbation and the occurrence of pneumonia (p<0.05). Moreover, a tentative correlation was observed between the use of ICS medication and the occurrence of pneumonia. A separate multivariate analysis revealed that advanced age, FEV1, ICS medication, and pneumonia were statistically significant independent factors related to exacerbation (p<0.05). The occurrence of concomitant pneumonia (HR = 3.353; p= 0.004) was found to be significantly linked with increased mortality (p<0.05) independently.[21]

However, there is one study that

contradicts the results of several studies that suggest that the use of inhaled corticosteroids has a greater risk of pneumonia than other agents in COPD. This study concluded that the use of inhaled corticosteroids does not increase the risk of pneumonia. Only 13.6% of patients treated with ICS progressed to pneumonia compared to 7.7% of patients treated without ICS. The drawback of this study is the variable dose that was not determined and mentioned from this study.[24]

The heightened vulnerability to pneumonia in patients diagnosed with COPD who are on ICS may be attributed to a confluence of factors, including immunosuppressive properties and the obstruction of pre-existing bacterial colonization in the airways.[25,26] Studies have shown that ICS can achieve higher concentrations within the lungs, and the potency of these medications is directly linked to an increased vulnerability to pneumonia. The documented immunosuppressive effects may weaken the natural ability to combat initial or subsequent bacterial infections, ultimately contributing to pneumonia.[27]

The observed differences within the same drug class, such as budesonide and fluticasone propionate, regarding pneumonia risk in COPD may be due to variations in the pharmacokinetics of these drugs. Specifically, fluticasone propionate has lower water solubility, resulting in a comparatively slower release from the fluid lining the airway lumen when compared to budesonide. This leads to a longer-lasting local immunosuppressive effect of fluticasone propionate compared to budesonide.[28]

CONCLUSION

In conclusion, the ICS administration in patients diagnosed with COPD is correlated with an increased incidence of pneumonia. Moreover, the frequency of pneumonia cases is directly proportional to the dose of ICS administered. The increased susceptibility to pneumonia reported in individuals undergoing treatment with fluticasone/salmeterol may be attributed to variations in immunosuppressive efficacy and the unique pharmacokinetic and pharmacodynamic characteristics of budesonide and fluticasone. We think that the use of ICS/LABA combination remains effective with consideration of adequate dosing, as well as the characteristics of patients who are susceptible to the risk of future infections. Therefore, the need for continuous therapy monitoring to minimize the occurrence of side effects in the form of pneumonia in the future.

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