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**REVIEW ARTICLE**

# Risk of Pneumonia with Inhaled Corticosteroid/ Long-Acting β2 Agonist Therapy in Chronic Obstructive Pulmonary Disease

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## ABSTRACT

**Aim:** To determine the pneumonia risk in COPD patients, which treatment is more effective to prevent patients to develop more complex situation.

**Method:** This randomized study design was conducted from September 2022 to December 2022 and approval by the ethical committee of the Hospital was obtained. All the participants were 45 to 65 years old. Patients were receiving a combination of medicine whereas the first group had 51 patients receiving low-dose fluticasone propionate 250 µg and salmeterol 50 µg twice in a day. The second group was receiving high-dose treatment of fluticasone propionate 500 µg and salmeterol 100 µg twice a day. Clinical follow-up proceeded for complete assessment and for safety measures. It also includes vital sign measurements such as heart rate, pneumonia, bone fracture, and hematological measurement. In the case of suspected pneumonia, moderate to severe exacerbation event chest radiography was performed. For statistical analysis two software are used one is statistics 8.1 and the other is Pad prism version 5. One Way ANOVA is applied.

**Results:** A total 110 number of patients aged 45-65 were recruited for this study. From the total of 110, eight persons are excluded due to cystic fibrosis, pulmonary fibrosis, and bronchiectasis. 102 patients are part of this study out of which 33(32.35%) were females and 70(67.64%) were males. Patients with smoking history were 40(39.21%), history of moderate and severe exacerbations were 20(19.60%) and 8(7.84%). Patients of group one who were receiving low doses of fluticasone propionate 250µg and salmeterol 50µg shows improvement in the patient condition and at the eight week of treatment dose the results are, moderate exacerbation was found in 12(23.52%) patients with 95% CI=1.89-2.30, severe exacerbation in 6(11.76%) with 95% confidence intervals, and pneumonia in 6(11.76%) with 95% CI=1.71-1.67.Group two follow-up also shows improvement in patients' health status but it also increases the chances of pneumonia development. At eight week moderate exacerbation was found in 7(13.72%) patients with 95% CI=3.00-0.34, severe exacerbation in 4(7.84%) with 95% confidence intervals 3.06-0.56, and pneumonia in 9(17.64%) with 95% CI= 3.08-0.66. All the factor's p-value was statistically significant. As the number of pneumonia, patients was higher in group two patients as compared to group one.

**Practical implication:** Pneumonia is more likely to occur in patients with chronic obstructive pulmonary disease (COPD). The frequency of acute episodes of symptom exacerbation is decreased by inhaled corticosteroids. Low dose therapy is more effective than the high doses effective in patients. This research article helps to aware the society about the risk factors and their treatment.

**Conclusion:** we concluded that COPD patients are more vulnerable to developing pneumonia even if we used the ICS therapy in combination with long-acting β2 agonist therapy. Low dose therapy is more effective than the high doses effective in our study

**Keywords:** chronic obstructive pulmonary disease COPD, Inhaled corticosteroids (ICS), Long-acting bronchodilators

## INTRODUCTION

Globally, chronic obstructive pulmonary disease COPD is diagnosed in a large number of people as per estimated it affects more than 200 million people[1]. In the USA it has become 3rd leading reason for the increased mortality rate. The research predicted that COPD can be a frequent cause of death across the world by 2030[2]. Mostly, COPD brings the change alveolar by its destruction, limitation of airflow, and loss of elastic coiling leading to develop hyperinflation with insufficient emptying of lungs on exhalation[3,4]. Long-acting bronchodilators used in patients with moderate and more severe symptoms of chronic obstructive pulmonary disease[5]. The best management for the treatment of COPD prefers to use these agents in its treatment maintenance. The inhaled long-acting bronchodilators such as $\beta_2$ agonists help to smooth the muscles and enhanced the lung's functional capacity[6].

In patients with COPD and chronic bronchitis, short-term investigations using ICS monotherapy in the 1990s discovered that anti-inflammatory medication reduced bronchial inflammation but had varied effects on lung-function measurements of forced expiratory volume in 1 second (FEV1) and peak expiratory flow (PEF)[7,8]. In a 6-month research, patients receiving ICSs experienced fewer exacerbations overall, and especially the most severe exacerbations. In order to ascertain the impact of treatment on the pace of pulmonary function loss, four long-term (3-year) randomised, placebo-controlled investigations of ICS in patients with COPD were carried out[9,10]. A meta-analysis of ICS studies investigating lung function in patients with COPD showed that ICS use did not slow the rate of $FEV_1$ decline in 3,571 patients over 24–54 months. In addition, a subsequent pooled analysis of 3,911 patients showed that after 6 months, ICS therapy did not modify $FEV_1$ decline in patients with moderate-severe COPD. 1,277 smokers aged 30-65 years who had prebronchodilator FEV1 slow vital capacity ratio 70% and postbronchodilator. FEV1 50%–100% expected were randomly assigned to either budesonide dry-powder inhaler or a placebo for three years. Asthma-related patients were not allowed to participate. Over the first six months, there were significant differences in the post-bronchodilator FEV1 changes between ICSs (improved at a rate of 17mL/year) and placebo (declined by a rate of 81mL/year, P0.001); however, by nine months, the slopes of FEV1 decline were comparable between treatment groups (P=0.39). The median reduction in FEV1 over 3 years among those who successfully completed the 3-year study (n=912) was 140mL in the ICS group and 180mL in the placebo group (P=0.05). ICS was more effective in patients who smoked less[11,12].

In another study by using the ICS-LABA combination compared to a placebo, the risk of death was decreased by 17.5% among 6,184 randomised patients (P=0.052). In comparison to

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either component alone or placebo, ICS-LABA significantly reduced the rate of exacerbations by 25% (P 0.001) and improved health status and FEV1. Patients with COPD aged 40 years or older who had at least a 10-pack-year smoking history, a FEV1:FVC ratio below 0.70, a FEV1 below 50% of predicted, and at least one exacerbation in the previous year requiring oral CSs, antibiotics, or hospitalisation were included in a later double-blind, randomised, parallel-group study[13,14,15].

In 2003, an evaluation of three ICS-LABA combination-therapy studies in COPD patients, a 30% reduction in exacerbations was found vs placebo and trough FEV1 improved vs placebo (101 mL/year, 95% CI 76-126) or either therapeutic drug alone (ICS 50 mL/year, 95% CI 26-74; LABA 34 mL/year, 95% CI 11-57) (15).LABA or ICS monotherapy was compared to ICS-LABA combination therapy delivered in a single inhaler in two Cochrane database systematic reviews. The exacerbation rate was decreased by 24% (95% CI 0.68-0.84) across nine eligible studies comparing ICS-LABA to LABA alone, although mortality did not differ (OR 0.92, 95% CI 0.76-1.11).ICS-LABA considerably reduced the rate of exacerbations by 13% (RR 0.87, 95% CI 0.80-0.94) in six studies comparing it to ICS monotherapy, and combination therapy significantly decreased the risk of death (OR 0.78, 95% CI 0.64-0.94). Additionally, a 2014 Bayesian network meta-analysis of fixed-dose ICS-LABA combinations with active control or placebo and randomised controlled trials of at least 12 weeks duration found that ICS-LABA reduced moderate-to-severe exacerbations, with the exception of beclomethasone dipropionate-formoterol, which had the smallest sample size of any group[15,16,17].

Inhaled corticosteroids (ICS) are used in combination as a second-line option to reduce the frequent extraction in chronic obstructive pulmonary disease. Instead of this, it is estimated that more than 70% of people are treated with high doses of ICS. Moreover, research shows that high doses could develop skin bruising, cataract, osteoporosis, bone fracture, and adrenal suppression[8]. On the other hand, adverse effects of ICS used reported higher chances of pneumonia development in patients with COPD. There are conflicts in pieces of evidence of CSI therapy as studies suggested that its magnitude varies for pneumonia risk associated with fluticasone propionate. This makes the situation complex while making treatment decisions[18,19,20].

## METHODOLOGY

This randomized study design was conducted from September 2022 to December 2022 and approval by the ethical committee of the Hospital was obtained. All the participants were 45 to 65 years old. The patients were admitted to the hospital after the clinical assessment to get proper treatment under observation if needed.

**Patients:** The patients who were diagnosed with COPD were defined with stages III and IV according to the global initiative for chronic obstructive lung disease in which post-bronchodilator $FEV_1$ predicted less than 50%. People with $FEV_1$/FCV of 60% predicted or less, had a smoking history, previous history of exacerbations (moderate to severe). If patients showed worsening COPD symptoms that needed change in the treatment plan and medication, it might be an alteration in the prescribed dose or introduction to new drugs. In the case of the more critical condition of COPD patients could be shifted into emergencies for treatment. A record of each episode of exacerbation was kept in his/her report. Informed consent was signed by patients and attends to before the start of treatment**.**

Patients were receiving a combination of medicine whereas the first group had 51 patients receiving low-dose fluticasone propionate 250µg and salmeterol 50µg twice in a day. The second group was receiving high-dose treatment of fluticasone propionate 500 µg and salmeterol 100µg twice a day. Clinical follow-up proceeded for complete assessment and for safety measures. It also includes vital sign measurements such as heart rate, pneumonia, bone fracture, and hematological measurement. In the case of suspected pneumonia, moderate to severe exacerbation event chest radiography was performed.

**Exclusion criteria:** Patients needed organ transplants, and chemotherapy, and had issues with acquired immunodeficiency syndrome. Patients with cystic fibrosis, pulmonary fibrosis and bronchiectasis. Patients who were already taken COPD therapy or hospital admission with a change in COPD therapy after the first visit were excluded from this study. Patients suffering from other lungs disorder were also removed from the study.

**Statistically Analysis:** Statistically, analysis was performed in software statistics 8.1. Data were presented in percentages and pair T- TEST and ONE WAY ANOVA was applied to the collected data. P-value greater than 0.05 shows non-significance results and a value less than 0.05 shows a significant response. Another software which is PAD PRISM version 5 was applied for graphical presentation.

## RESULTS

A total 102 number of patients aged 45-65 were part of this study of which 33(32.35%) were females and 70(67.64%) were males. Patients with smoking history were 40(39.21%), history of moderate and severe exacerbations were 20(19.60%) and 8(7.84%) (Table 1).

Figure 1: Enrollment of Patients and Completion of the Study

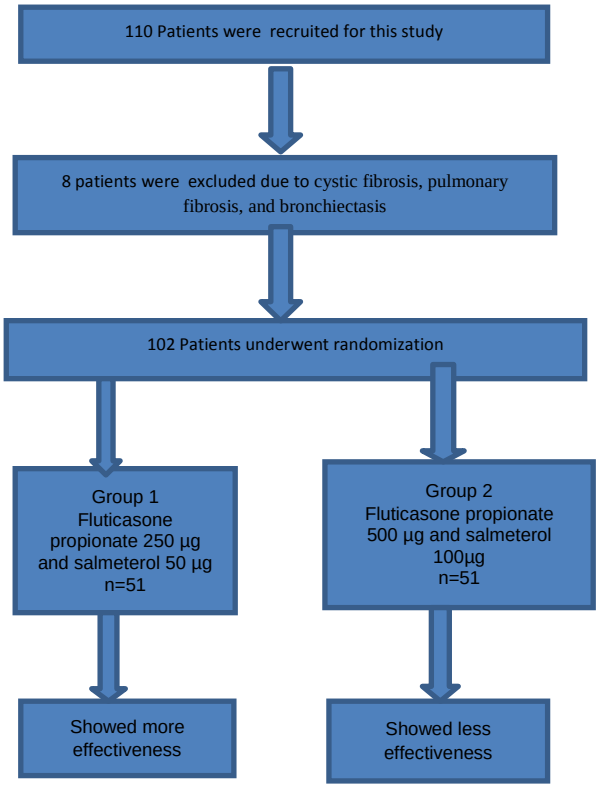


Table.1 General Characteristics of COPD patients (n=102)

| Characteristic | n |
|---|---|
| Age years | 45-65 |
| Females | 33 (32.35%) |
| Males | 70 (67.64%) |
| Smoking status | 40 (39.21%) |
| History of Moderate exacerbation | 20 (19.60%) |
| History of Severe exacerbation | 8 (7.84%) |

Table 2 presents the Group 1 which consists of 51 patients follow up of 8- weeks, they had received the fluticasone propionate 250 µg and salmeterol 50 µg. In their follow-up plan of two weeks 25(49.01%) patients were found with moderate exacerbation, 95% Cl= 1.92-18.07, a severe exacerbation was found in 10(19.60%), 95% Cl = 1.09-13.81, pneumonia was reported in 1.0 (1.96%) patients with 95% Cl 0.07-10.12. In week four moderate exacerbation was noted in 23 (45.09%) cases with 95% Cl 0.08-14.14 value. Severe exacerbation was found in 8 (15.68%) patients with a 95% Cl 8 (15.68%) value. pneumonia was reported in 1.0 (1.96%) patients with 95% Cl 0.07-10.12. At the sixth week of follow up moderate exacerbation was observed in 15(29.41%) patients with 95% Cl = 1.56-6.23, severe exacerbation in 6 (11.76%) cases with 95% Cl 1.45-7.01, and pneumonia was noted in 4(7.84%) patients with 95% Cl = 1.95-4.17. At eight weeks moderate exacerbation was found in 12 (23.52%) patients with 95% Cl = 1.89-2.30, severe exacerbation in 6 (11.76%) with 95 % confidence intervals, and pneumonia in 6 (11.76%) with 95% Cl = 1.71-1.67. Patients of group one who were receiving low doses of fluticasone propionate 250µg and salmeterol 50µg shows improvement in the patient condition but also developed pneumonia in some patients.

Table 2 also presents group 2, 51 patients with a follow-up of 8- weeks, had received the fluticasone propionate 500 µg and salmeterol 100 µg which was the double dose as compared to group one patients. In their follow-up plan of two weeks 20 (39.21%) patients were measured with moderate exacerbation, 95% Cl= 0.63-14.03, a severe exacerbation was measured in 8 (15.68%), 95% Cl = 0.74-13.05, pneumonia was not observed in any patients in the second week. In week four moderate exacerbation was reported in 18 (35.29%) cases with 95% Cl 0.97-11.02 value. Severe exacerbation was found in 9 (17.64%) patients with 95% Cl= 0.89-10.11 value. pneumonia was reported in 3 (5.88%) patients with 95% Cl= 0.10-13.81.

At the sixth week of follow up moderate exacerbation was observed in 11(21.56%) patients with 95% Cl = 0.80-3.47, severe exacerbation in 6(11.76%) cases with 95% Cl = 0.63-2.23, and pneumonia was noted in 5 (9.80%) patients with 95% Cl = 0.93-4.42. At eight weeks moderate exacerbation was found in 7(13.72%) patients with 95% Cl = 3.00-0.34, severe exacerbation in 4(7.84%) with 95% confidence intervals 3.06-0.56, and pneumonia in 9(17.64%) with 95% Cl = 3.08-0.66. All the factor's p-value was statistically significant. Group two follow-up also shows improvement in patients' health status but it also increases the chances of pneumonia development. As the number of pneumonia, patients were higher in group two patients as compared to group one.

Figure : 2 Graphical presentation of the exacerbation rate as group 1 shows the less risk of pneumonia with inhaled corticosteroid/ long-acting β2 agonist therapy in chronic obstructive pulmonary disease as compared to group two.

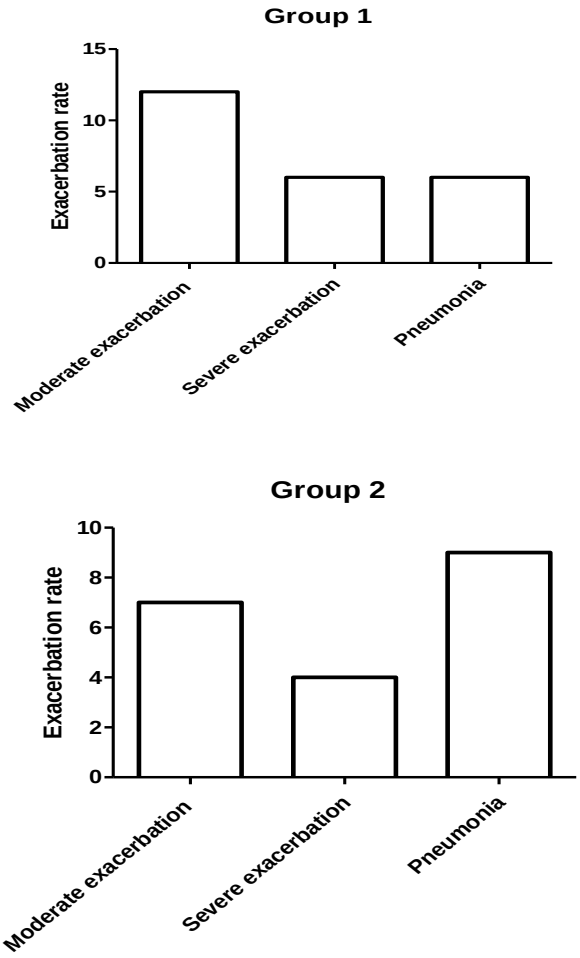


Table 2 Comparison between two groups of study to determine the risk of pneumonia

| Follow up | Group 1 fluticasone propionate 250 µg and salmeterol 50µg (n=51) | 95% Confidence interval | Group 2 fluticasone propionate 500 µg and salmeterol 100 µg (n=51) | 95% Confidence interval | p-value |
|---|---|---|---|---|---|
| **Week 2** | | | | | |
| Moderate exacerbation | 25 (49.01%) | 1.92-18.07 | 20 (39.21%) | 0.63-14.03 | 0.035 |
| Severe exacerbation | 10 (19.60%) | 1.09-13.81 | 8 (15.68%) | 0.74-13.05 | 0.035 |
| Pneumonia | 1.0 (1.96%) | 0.07-10.12 | 0.00 | 0.0-00.00 | 0.035 |
| **Week 4** | | | | | |
| Moderate exacerbation | 23 (45.09%) | 0.08-14.14 | 18 (35.29%) | 0.97-11.02 | 0.024 |
| Severe exacerbation | 8 (15.68%) | 0.12-11.01 | 9 (17.64%) | 0.89-10.11 | 0.036 |
| Pneumonia | 1 (1.96%) | 1.06-9.91 | 3 (5.88%) | 0.10-13.81 | 0.025 |
| **Week 6** | | | | | |
| Moderate exacerbation | 15 (29.41%) | 1.56-6.23 | 11 (21.56%) | 0.80-3.47 | 0.018 |
| Severe exacerbation | 6 (11.76%) | 1.45-7.01 | 6 (11.76%) | 0.63-2.23 | 0.018 |
| Pneumonia | 4 (7.84%) | 1.95-4.17 | 5 (9.80%) | 0.93-4.42 | 0.016 |
| **Week 8** | | | | | |
| Moderate exacerbation | 12 (23.52%) | 1.89-2.30 | 7 (13.72%) | 3.00-0.34 | 0.003 |
| Severe exacerbation | 6 (11.76%) | 1.63-1.82 | 4 (7.84%) | 3.06-0.56 | 0.004 |
| Pneumonia | 6 (11.76%) | 1.71-1.67 | 9 (17.64%) | 3.08-0.66 | 0.003 |

## DISCUSSION

COPD patients are more prone to develop pneumonia while high doses of ICS therapy are also associated to increase the risk of pneumonia. However, in the case of COPD, the progression of the disease from moderate to severe can lead to faster deterioration of pulmonary functions and increase the risk of mortality[21]. COPD has become a challenge for our healthcare systems and clinics[22]. The increase in COPD is because of exacerbations which can enhance the disease progression, lower the life quality and increase the economic burden especially, related to hospitalization[23].

An attempt to report the benefits of inhaled corticosteroids in COPD patients to reduce the risk by administrating lower doses that could be a more effective strategy to manage COPD patients[24]. In the current study we also found that the lower dose of CSI in combination with long-acting β2 agonist therapy is more effective than high-dose therapy.

In the current study, we had planned 8 week follow-up of prescribed medicine with regular checkups and hospitalization if required depending upon the patient's condition. We noted that pneumonia was strongly associated with inhaled corticosteroid/long-acting β2 during treatment. Patients who were taking high-dose treatment were greater in number with pneumonia problems as compared to low-dose treatment patients. Patients with chronic obstructive pulmonary disease (COPD) are at risk of exacerbations and pneumonia and the reduction of future exacerbation risk has become an important treatment objective . COPD management is therefore becoming like that of ischemic heart disease, where the aim is to reduce future risk as well as relieve current symptoms[24,25]. The management of ischemic heart disease benefits from the use of predictive equations, which use readily available clinical parameters to estimate risk of major cardiac events over the following 10 years. Similar risk equations may be helpful in COPD management[26,27].

Low forced expiratory volume in 1 second (FEV1), current smoking, and a history of prior exacerbations have all been shown to be risk factors for COPD exacerbations however a different study found no correlation between these two variables. Airway obstruction, low body mass index (BMI), older age use of psychoanaleptics presence of gastroesophageal reflux disease increased blood neutrophil counts and use of inhaled corticosteroids (ICS) are some of the factors linked to an increased risk of pneumonia in COPD. The impact of individual factors on the risk of pneumonia and COPD exacerbations has been studied. Even while some individual aspects might be pertinent, it seems more applicable to analyse numerous components[28,29,30,31].

Mixing medications with various mechanisms of action may lead to better results. There has been evidence of two-way synergistic activity between ICSs and LABAs. ICSs move glucocorticoid receptors from the cytoplasm to the nucleus as one of their biological functions. Without having to increase the ICS dosage, this activity is strengthened in the presence of -agonists and results in a stronger anti-inflammatory impact than either drug alone. Moreover, ICSs stimulate the production of additional -receptors by activating -receptor genes, boosting the bronchodilator effects of LABAs. Many clinical trials examining ICS-LABA combinations in patients with COPD have been undertaken, and their findings have been compiled in systematic reviews and meta-analyses to help guide therapy choices. The following sentences describe pertinent studies. The pivotal, double-blind, placebo-controlled, randomised Towards a Revolution in COPD Health (TORCH) trial compared salmeterol plus fluticasone propionate (50 and 500 g, respectively, given twice daily) with each component alone and placebo over a three-year period. Individuals with COPD were accepted if they had smoked for at least 10 packs a year, had a predicted FEV1 of 60%, and had a FEV1:FVC ratio of less than 0.70. Using the ICS-LABA combination compared to a placebo, the risk of death was decreased by 17.5% among 6,184 randomised patients (P=0.052). In comparison to either component alone or placebo, ICS-LABA significantly reduced the rate of exacerbations by 25% (P 0.001) and improved health status and FEV1. Salmeterol with fluticasone propionate (50 and 250 g, respectively) was found to have a 30.5% lower mean yearly rate of moderate-severe exacerbations among 782 randomised patients than salmeterol alone (P0.001) at half the fluticasone propionate dose used in the TORCH study [32,15]. To overcome the huge burden of COPD the main goal for effective management includes the precaution to prevent and lower exacerbations, relief from symptoms, and disease progression, and minimal side effects of treatment.

## CONCLUSION

In this study, we concluded and ensure that COPD patients are more vulnerable to developing pneumonia even if we used the ICS therapy in combination with long-acting β2 agonist therapy. Low dose therapy is more effective than the high doses effective in our study.

**Conflict of interest:** Nil

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