To Study the Ocular Side Effect by Chronic Use of Steroid in Chronic Obstructive Pulmonary Disease (COPD) Patients Attending Tertiary Care Centre in North India

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Abstract
Objective: To study the Ocular side effect by chronic use of steroid in Chronic obstructive pulmonary disease (COPD) attending tertiary care center in north India

Method: 500 COPD patients of age group 50 -90 years with minimum steroid exposure of 4 months and on inhaled corticosteroids were selected from TBCD and Ophthalmology department, S.N. Medical College and Hospital, Agra during the period of one year August 2017 to August 2018, a detailed clinical history, physical and ocular examination was done. Various investigations and diagnostic criteria were used during study. Average daily dose of inhaled corticosteroids was defined as low (1–250 µg), medium (251–500 µg), and high (501–1000 µg) using fluticasone propionate equivalents

Result: Out of 500 COPD patients, of which 58 were dropouts. We identified 78 cataract and 24 glaucoma patients with a prevalence of 17.64 % and 5.42% respectively. We also observed a dose-response relationship with the highest prevalence of cataract (39.74%) and glaucoma (41.6%) at daily doses of 501–1000 µg fluticasone propionate equivalents.

Conclusion: Both cataract and glaucoma are associated with Chronic use of high dose inhaled corticosteroid in COPD patients, cataract being the more commoner one, judicious use of such medication can prevent these manifestations.

Keywords: chronic obstructive pulmonary disease, steroid-induced cataract, steroid-induced glaucoma.
treatable. COPD is a major cause of chronic morbidity and mortality through the world, many people suffer from this disease for years and die prematurely from it or its complications. Globally, the COPD burden is projected to increase in coming decades because of continued exposure of COPD risk factors and ageing of population\(^2\) commonly used maintenance medication for COPD includes beta agonist, anticholinergics, inhaled corticosteroids, oral glucocorticoids, PDE4 inhibitors, Antibiotics, mucolytics/antioxidants, although chronic and high dose of any medication can be harmful, our study is concerned about ocular side effect of steroid more specifically cataract and glaucoma.

Cataract and glaucoma have been the leading causes of blindness worldwide. Age-related cataracts are responsible for 51% of world blindness, or approximately 20 million people. Glaucoma is the second leading cause of blindness worldwide\(^3\) Globally there are estimated 60 million people with glaucomatous optic neuropathy and an estimated 8.4 million people who are blind as a result of glaucoma, these numbers are set to increase to 80 million and 11.2 million by 2020. The increasing use of corticosteroids in various medical conditions also increases the steroid-related complications of ocular concern, particularly steroid-related cataract and glaucoma, constituting the global burden of visual impairment worldwide. Steroid use is the fourth leading risk factor for secondary cataract and accounts for 4.7% of all cataract extractions.\(^4\) The association of steroids and glaucoma was first established in 1950 when systemic administration of the adrenocorticotrophin hormone was shown to increase intraocular pressure (IOP).\(^5\) Steroid-induced glaucoma is a form of secondary open-angle glaucoma occurring as an adverse effect of corticosteroid therapy.\(^6\) It is usually associated with topical steroid use, but it may develop with oral, intravenous, inhaled, and periocular steroid administration by causing a decrease in aqueous outflow facility.

There is limited number of studies depicting relationship between chronic inhaled corticosteroid use and its ocular complications. The aim of our study was to determine the prevalence of inhaled steroid-induced glaucoma and cataract in patients with chronic obstructive pulmonary disease (COPD) attending a tertiary care center and also to find a dose-related response of steroid-induced cataract and glaucoma in COPD patients.

**Materials and Methods**

Our study was conducted with the approval of our local ethics committee and in accordance with the tenets of the Declaration of Helsinki. Written consent was obtained from all study subjects. All known cases or diagnosed cases of COPD as per criteria adopted and standardized by WHO-GOLD 2018, We evaluated 500 patients for study after given their informed consent aged 50 years or older and had received steroid therapy for at least 4 months during a period of 1 year from August 2017 to August 2018. An inclusion criterion include- COPD patients receiving minimum of 4 month inhaled corticosteroid therapy in a year, Exclusion criterions include Already diagnosed cases of glaucoma or cataract before steroid intake, any other cause of glaucoma and cataracts other than steroids and any other cause of diminution of vision, namely retinal pathology, corneal pathology, uveitis, COPD patients with other comorbidities such as diabetes mellitus, hypertension, and prescribed steroid therapy for other systemic illness.

A detailed ocular examination was performed including history, thorough anterior and posterior segment evaluation using slit lamp biomicroscopy, automated visual field testing for subjects with best-corrected visual acuity better than 6/60 in the better eye using the 30-2 test pattern on Humphrey Visual Field Analyzer (Carl Zeiss Meditec, Bangalore, India), gonioscopy, indirect ophthalmoscopy, and disc evaluation using a +90 D Volk lens (New Delhi, India).
All the COPD patients are grouped into 3 category based on duration and daily dosage of inhalational fluticasone propionate or its equivalent as mild, moderate, and high dosages. Shown in Table 1. In our study, mainly fluticasone propionate and budesonide were prescribed as inhaled steroids in combination with long-acting beta agonist. The maximum prescribed daily dosage of fluticasone is 500 μg twice daily, and budesonide is 720 μg twice daily.

**Result**

Of the 500 diagnosed COPD patients, 58 subjects dropped out during the study period. The subjects comprised 318 (72%) men and 124(28%) women [mean (SD) age, 64.12 (8.02) years; age range, 52–85 years], with a male-to-female ratio of 2.57:1 (Fig. 1). In this study, 34.16% of cases were aged 51–60 years, 38.91% were 61–70 years, 20.13% were 71–80 years, and 6.78% were 81–90 years. The maximum number of women was in the group aged 51–60 years (52.41%), and the highest number of men was recorded in the group aged 61–70 years (42.76%). The age-sex distribution of the study population is shown in Table 2 and Figure 2. Of 442 COPD patients, 78 patients had steroid-induced cataract, including 60 men and 18 women. The overall prevalence of steroid-induced cataract was found to be 17.64%, including 21 men and 3 women (Fig. 3). Seventy-seven subjects had IOP greater than 22 mm Hg and out of these, 24 patients developed steroid-induced glaucoma with glaucomatous disc changes and field defects. The percentage of the population who had only glaucoma was 1.80%, and the percentage of the population who had only steroid-induced cataract was 3.52%. Thirty-six patients had a positive family history of glaucoma. It was found that the highest prevalence of steroid-induced glaucoma (8.13%) was in the age group of 61 to 70 years, whereas the lowest prevalence rate (2.64%) was noticed in the age group of 51 to 60 years. The prevalence of steroid-induced glaucoma with demographic details is shown in Table 5. We also observed that men in our study had a higher prevalence of steroid-induced cataract (18.86%) than women (14.51%). The prevalence of steroid-induced cataract increased significantly with age from 11.25% among those aged 51 to 60 years to 23.33% among those aged 80 years or older. The prevalence of steroid-induced cataract with demographic details is shown in Table 3.

The prevalence of steroid-induced cataract was higher in the group of patients taking moderate (251–500 μg/d fluticasone propionate or its equivalents) to high doses (500–1000 μg/d fluticasone propionate or its equivalents) of inhaled corticosteroids (ICS) on a daily basis: 32.05% (n = 25) and 35.89% (n = 28), respectively. No cataract was found in patients taking low doses (1–250 μg/d fluticasone propionate or its equivalents) of ICS, even for more than 1 year’s duration. The lowest prevalence rate (3.8%) was found in the group taking a high dosage of inhalational steroids for 4 to 6 months, whereas the highest prevalence rate (35.89%) was observed in the group taking a high dosage of ICS for more than 1 year. Figure 4 and Table 4 depict the dose-response relationship. In our study, the overall prevalence of steroid-induced glaucoma was found to be 5.42%, including 21 men and 3 women (Fig. 5). Seven subjects had IOP greater than 22 mm Hg and out of these, 24 patients developed steroid-induced glaucoma with glaucomatous disc changes and field defects. The percentage of the population who had only glaucoma was 1.80%, and the percentage of the population who had only steroid-induced cataract was 3.52%. Thirty-six patients had a positive family history of glaucoma. It was found that the highest prevalence of steroid-induced glaucoma (8.13%) was in the age group of 61 to 70 years, whereas the lowest prevalence rate (2.64%) was noticed in the age group of 51 to 60 years. The prevalence of steroid-induced glaucoma with demographic details is shown in Table 5. We also observed that men in our study had a higher prevalence of steroid-induced glaucoma (6.60%) than women (2.4%). Of 24 patients diagnosed with steroid-induced glaucoma, none were in the group receiving 4 to 6 months of steroid therapy even at a high dose. The highest prevalence (n = 10; 41.6%) was noticed in the group receiving a high dosage of inhalational therapy for more than 1 year’s duration. The lowest prevalence rate (n = 4; 16.6%) was observed in the group of patients taking moderate to high doses for 6 months to 1 year. Even patients taking moderate doses of inhalational steroids for more than 1 year showed...
a prevalence rate of 25% (n = 6). Details of the dose response relationship of steroid-induced glaucoma are shown in Figure 5 and Table 6. Five eyes showed advanced glaucomatous cupping with significant field changes, and all of them were taking high doses of steroid therapy (501–1000 µg/d fluticasone propionate or its equivalents) for more than 1 year.

Table 1 Distribution of Patients by Duration and Dosage of Inhalational Steroids

| Inhalational dosage of Fluticasone propionate or equivalent | Duration |
|-----------------------------------------------------------|----------|
| Mild dosage, 1-250 ug/d                                   | 4 -6 mo  |
| Moderate dosage, 251-500 ug/d                             | 6mo -1 yr|
| High dosage, 501-1000 ug/d                                | >1yr     |

Table 2 Age-Sex Distribution of the Study Population

| Age group | Men (n= 318) | Women (n= 124) | Total (n=442) |
|-----------|--------------|----------------|---------------|
| 51-60     | 86(27.04%)   | 65(52.41%)     | 151(34.16%)   |
| 61-70     | 136(42.76%)  | 36(29.03%)     | 172(38.91%)   |
| 71-80     | 68(21.38%)   | 21(16.93%)     | 89(20.13%)    |
| 81-90     | 28(8.80%)    | 2(1.61%)       | 30(6.78%)     |

Table 3 Association of Steroid-Induced Cataract with Sociodemographic Characteristics (Age Groups)

| Age group | No. subjects examined | No. Steroid induced Cataract patients | Prevalence(%) |
|-----------|-----------------------|--------------------------------------|---------------|
| 51-60     | 151                   | 17                                   | 11.25%        |
| 61-70     | 172                   | 35                                   | 20.34%        |
| 71-80     | 89                    | 19                                   | 21.34%        |
| 81-90     | 30                    | 7                                    | 23.33%        |
| overall   | 442                   | 78                                   | 17.64%        |

Table 4 Dose-Response Relationship of Steroid-Induced Cataract

| Inhalational dosage of fluticasone propionate or equivalent | 4-6 mo | 6mo -1 yr | >1yr | Total number cataract patient |
|-------------------------------------------------------------|--------|-----------|------|--------------------------------|
| Mild dosage, 1-250ug/d                                       | -      | -         | -    | -                             |
| Moderate dosage ,251-500ug/d                                 | -      | 7(8.97%)  | 25(32.05%) |
| High dosage, 501-1000ug/d                                   | 3(3.8%) | 15(19.23%) | 28(35.89%) |

Table 5 Association of Steroid-Induced Glaucoma With Sociodemographic Characteristics (Age Groups)

| Age group | No. subjects examined | No. Steroid induced glaucoma patients | Prevalence(%) |
|-----------|-----------------------|--------------------------------------|---------------|
| 51-60     | 151                   | 4                                    | 2.64%         |
| 61-70     | 172                   | 14                                   | 8.13%         |
| 71-80     | 89                    | 4                                    | 4.49%         |
| 81-90     | 30                    | 2                                    | 6.66%         |
| overall   | 442                   | 24                                   | 5.42%         |

Table 6 Dose-Response Relationship of Steroid-Induced Glaucoma

| Inhalational dosage of fluticasone propionate or equivalent | 4-6 mo | 6mo -1 yr | >1yr | Total number Glaucoma patient |
|-------------------------------------------------------------|--------|-----------|------|--------------------------------|
| Mild dosage, 1-250ug/d                                       | -      | -         | -    | -                             |
| Moderate dosage ,251-500ug/d                                 | -      | 4(16.6%)  | 6(25%) |
| High dosage, 501-1000ug/d                                   | -      | 4(16.6%)  | 10(41.61%) |
**Figure 1** - Sex distribution of the study population.

- Male: 72%
- Female: 28%

**Figure 2** - Age-sex distribution of study population

- Age groups: 51-60, 61-70, 71-80, 81-90
- Sex distribution:
  - 51-60: Male 27.04%, Female 52.41%
  - 61-70: Male 29.03%, Female 42.76%
  - 71-80: Male 21.38%, Female 16.93%
  - 81-90: Male 8.8%, Female 1.61%

- Total population: 442
- Steroid induced cataract: 78
Figure 3 Prevalence of Steroid induced cataract and glaucoma

Figure 4 Dose response relationship of steroid induced cataract

Figure 5 Dose response relationship of steroid induced Glaucoma.
Discussion
Corticosteroids are a class of anti-inflammatory drugs commonly used to treat various ocular and systemic conditions. Prolonged use of inhaled glucocorticoids is a significant risk factor for the development of various ocular manifestations. In our study, we evaluated the effect of inhaled corticosteroids on COPD patients with respect to duration of therapy and dosage of each patient. Garbe E, Suissa S, LeLorier J⁷, found in their study that prolonged administration of high doses of inhaled corticosteroids increases the likelihood of undergoing cataract extraction in their study. They found use of inhaled corticosteroids for more than 3 years was associated with undergoing cataract extraction (odds ratio [OR], 3.06; 95% confidence interval [CI], 1.53-6.13) in our study of 442 COPD patients, we also observed a positive association between ICS and PSC, with a prevalence of 17.64% after excluding diabetes mellitus, systemic hypertension, and other systemic illness. Additionally, a positive dose-response relationship was observed between the dosage of inhaled steroids and the prevalence of steroid-induced cataract, with the highest prevalence (35.89%) found in the group taking inhaled fluticasone propionate or its equivalents in daily doses ranging from 500 to 1000 μg/d for more than 1 year’s duration. In our study, the inhaled steroids prescribed to the patients were mainly fluticasone propionate and budesonide. No beclomethasone was prescribed to any of the subjects in the study population. This result is also supported by study of Smeeth et al.⁸ however, Miller et al⁹ found that neither cataract nor glaucoma were associated with a fluticasone propionate/salmeterol fixed-dose combination or other ICS exposure, dose-response relationship was also not observed in this population-based nested case-control study of COPD patients in the United Kingdom. Some studies conducted in children too Tinkelman et al¹⁰ found no cataracts in 108 children treated with inhaled beclomethasone for 1 year. Nassif et al¹¹ identified 1 PSC among 32 children treated with inhaled corticosteroids for an average of 1.3 years. In our study, the prevalence of steroid-induced glaucoma was 5.42%. Seventy-seven subjects had IOP greater than 22 mm Hg, and 24 patients developed steroid-induced glaucoma with field and optic nerve head changes. Of 77 subjects, 36 patients had a positive family history of glaucoma. The highest prevalence (41.61%) was noticed in the group receiving heavy doses of inhalational therapy (500–1000 μg/d fluticasone propionate or its equivalents) for more than 1 year. This result is supported by Mitchell et al¹² who reported an association between ICS use and glaucoma among patients with a family history of glaucoma or elevated IOP.
Age and sex also have an impact in the causation of ocular morbidity from inhaled steroids, as is evident from our study. The prevalence of steroid-induced cataract increased significantly with age from 11.25% among those aged 51 to 60 years to 23.33% among those aged 80 years or older. Similarly, the highest prevalence of steroid-induced glaucoma (8.13%) was in the age group of 61 to 70 years, sex predilection, male preponderance was found both in steroid-induced cataract and glaucoma. In steroid-induced cataract subjects, men had a higher prevalence of steroid-induced cataract (18.8%) than women (14.51%). Similarly, the prevalence of steroid-induced glaucoma was higher in men (6.6%) compared with women (2.4%).
The limitation of our study was the failure to obtain a detailed history of oral corticosteroids used by a limited number of subjects in the study population and to analyze their role in the development of steroid-induced cataract and glaucoma. And the number of subjects with COPD and the duration of our study were too small to draw definite conclusions.

Conclusion
Steroid-induced ocular complications majorly comprising of cataract and glaucoma, is an iatrogenic and preventable disease. The
unwarranted and irrational use of steroids especially in developing countries by local medical practitioners as well as unmonitored self-use by patients themselves points to a lack of awareness about the disease. It is evident from our study that higher doses and longer duration of inhaled corticosteroid in patients with COPD are associated with a higher prevalence of cataract and glaucoma.

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