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Research Article

ROLE OF STEROIDS IN STABLE PATIENTS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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A R T I C L E I N F O

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A B S T R A C T

Background: Corticosteroids are widely used in the treatment of allergic and inflammatory conditions. It is important to recognize that there are great species differences in the responses to glucocorticoids and that means a "Steroid resistant" species. Steroids affect metabolism and distribution of T and B lymphocytes, but do not significantly affect antibody production in humans. Steroids profoundly affect the inflammatory response by way of vasoconstriction, decreased chemotaxis and interference with macrophages. There are still enormous gaps in our knowledge of the action of glucocorticosteroids in stable patients of chronic obstructive lung disease (COPD).

Aim: To find out the effect of steroids on pulmonary function and arterial blood gases in stable patients of chronic obstructive pulmonary disease and to know the clinical improvement in such patients by giving steroids.

Material and Methods: This study was done in the department of General Medicine (SKIMS) from August 2017 to January 2019 on patients of stable chronic obstrucImonarydisense. A total number of 100 patients were enrolled for the study but 20 patients, 10 from each group lost their follow up.To see the effect of steroids on pulmonary function tests and Arterial blood gases, patients were divided into case and control group.Patients in case group were gives prednisolone 30 mg orally for two week (tapering dose). Patients in control group were given placebo for the same duration of two weeks. Steroid response was defined as 15% improvement in baseline FEV.

Results and Conclusion: Steroid response was defined as 15% increase in FEV1/FVC after receiving tapering dose of prednisone 30 mg for 2 weeks. None of patients in case group showed increase in FEV1/FVC of 15%. The change in pulmonary function tests and arterial blood gases were comparable in each group (p>.0.5). So steroids in stable patients of COPD, are best to be avoided.

INTRODUCTION

COPD is a leading cause of death worldwide, with an estimated prevalence of almost 10% in adults aged ≥40 years.[1]Chronic obstructive disease has been defined by the American Thoracic Society as a disease state characterized by the presence of air flow obstruction secondary to chronic bronchitis or emphysema.[2]Chronic bronchitis is defined for epidemiologic purposes as the presence of chronic cough for 3 months in each 2 successive years ,infection with mycobacterial tuberculosis, carcinoma of lung or congestive failure have been excluded.[2]Emphysema on the other hand is defined pathologically as abnormal air space enlargement.[3,4]

Historical Background: Theappearance of enlarged respiratory air space the surfaces of lung was first illustrated by Ruysch in 1691, later in the 18th century, Mathew Baillic provided the earliest illustration and a brief description of emphysema.

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In the early 19th century, laeuheci using air dried inflated lung specimens gave description of emphysema which stood in its essentials for 125 years

Natural History of COPD.[5,6]

The FEV1 of patients with COPD decreases around 90ml a year. The lung heath study showed that patients who stopped smoking had a mean post bronchodilator FEV1 increase of 57ml at first annual visik compared with a mean FEV1 decline of 38ml for those who continue to smoke.

Pathology

Chronic bronchitis is associated with hypertrophy of mucus producing blands found in the submucosal of large cartilaginous airways. In lungs from patients with chronic obstructive lung disease which have been studied at postmortem, the major site of airflow obstruction has been shown to be in the small airways. Goblet cell hyperplasia, mucosal and submucosal inflammatory cells, edema peribronchial fibrosis, intraluminal mucus plugs and increased smooth muscle are characteristic finding in small airways.The

alveolar epithelium I both the target and the initiator of inflammation in chronic bronchitis. Bronchial inflammation differs from the predominantly eosinophils and inflammation of asthma because of the predominance of neutrophil's and the peribronchial location of fibrotic changes. It is the consequence of the action of interleukin-8 and a variety of other chemotactic and proinflammatory cytokines and of colony, stimulating factors releaser by airway epitheal cells in respone to toxic, infectious or inflammatory stimuli.Chronic bronchitis is characterized pathologically by hypertrophy of submucin glands found in submucosal of lung cartilaginous airways; which is indicated by reid index.[7,8,9]

Normal Reid index is 0.44
Patients with COPD have a RI of 0.52

Emphysema Has two Variants

1. Centriacunar
2. Panacinar

Centriacinar emphysema is characterized by distention and destruction limited to respiratory bronchioles with less changes in the periphery of acirus. Panacinar emphysema. Both central and portions of lungs are involved.[3,10]

Risk Factors of COPD

Established

- ✓ Cigarette smoking.[11]
- ✓ Occupational exposure
- ✓ α1 antitrypsin deficiency

Probable

- ✓ Air pollution
- ✓ Poverty
- ✓ Childhood exposure to smoke
- ✓ Hyperactive airways
- ✓ Alcohol

Possible

- ✓ Low birth weight
- ✓ Childhood respiratory infections
- ✓ Family history
- ✓ Atopy
- ✓ IGA nonserector
- ✓ Blood group A

Pulmonary Function tests.[3,2,12]

Roughly comparable information can be obtained from the peak flow measurement or from the forced expiratory flow volume level.None of these tests can distinguish between chronic bronchitis andemphysema.

The FEV, and FEV/FVC ratio fall progressively as the severity of COPD increases. In the laboratory about 30% of patients have an increase of 20% or more in their FEV, following a ß-agönist, Ipratropium bromide treatment. Lung volume measurements show an increase in total lungs capacity, functional residual capacity and residual volume. The vital capacity may be decreased.

Arterial blood gases.[13]Arterial blood gases reveal hypoxemia without hypercapnia in the early stages. As the decline progresses, hypoxemia becomes more severe and hypercapnia supervenes.

Management of Patients with COPD.[14,15,16]

- Smoking cessatlon
- Pharmactogletherupy
- iii)Vacination

Pharmacologic therapy.[2,14]

The different drugs used in management of COPD are

β-Agonists
a) Bronchodilators
Anticholinergic drugs
Methylxanthines

b) Corticosteroides

Pathogenesis of COPD3

COPD evolves from an inflammatory process involving the airwaysand distal airspaces. Increased activity of oxidants combined withdecreased activity of antioxidants, tormcdoxidative stross, have beeriimplicated in the development of inllammation und COPD. The submucosa of small airway in patients with COPD hasincreased numbers of CD8 lymphocytes and eosinophils, macrophagesand mast cells. Neutrophils are increased in smokers, but their numberdo not correlate with the presence of airflow obstruction. Patients withchronic airflow obstruction show higher levels of myeloperoxidase andeosinophilic cationic protein than do patients with normal airflow.Macrophages and mast cells produce transforming growth factor BTGF-B), a peptide related to fibrogenesis. Patients with chronic airflowobstruction show a twofold elevation of TGF- in lavage liquid; theamount of TGP- showasignificant negative correlation with FE theforced expiratory volume in one second). Smoke also leads to lipidperoxidation and to DNA damage.

Corticosteroids in COPD.[1,7,17,18,19,20,21]

Mechanism of action of Steroids

Corticosteroids are widely used in the treatment of allergic andinflammatory conditions. It is important to recognize that there aregreat species differences in the responses to glucocorticoids and thatmanis a "Steroid resistant" species. Steroids affect metabolism anddistribution of T and B lymphocytes, but do not significantly affectantibody production in man. Steroids profoundly affect theinflammatory response by way of vasoconstriction, decreasedchemotaxis and interference with macrophages. Steroids affect typeI, Ill and IV mechanisms of immunologic injury. There are still enormousgaps in our knowledge of the action ofglucocorticosteroids.Studies done by Fan VSGaziano JM, Lew R, *et al*[18]showed that use of oral steroids showed no differences in rates of rehospitalisation.

In a neta analysis of all English Language Placebo controlledtrials of oral steroids in COPD published between 1966 and 1989,10 studies met 9 prospectively defined standard. The response tooral corticosteroids was defined as 20% improvement in base FEV,and the number of patients who responded were separated fromthose who responded to placebo. Overall 10% of patients fulfilledthe criteria for response. No association was found betweencorticosteroid response and clinical features such as age or baselineFEVI. The use of inhaled corticosteroids in COPD patients

holdssome promise but at present has not been demostrated conclusively.Studies have shown that patients receiving oral corticosteroids havea 20% or greater increase in FEV, only 10% more often thanpatients s receiving Placebo. Long term systemic glycocorticoid use isassociated with worsened osteoporosis and increased risk ofvertebral fracture, It systemic "torolds are uscd the lowest doseshould be employed and ulteuteduy dosing used whenever possible.

Hence present study was undertaken with an objective to find out the effect of steroids onpulmonary function and arterial blood gasesin stable patients of chronic obstructivepulmonary disease and to know the clinicalimprovement in such patients by givingsteroids

MATERIAL AND METHODS

This study was done in the department of General Medicine (SKIMS) from August 2017 to January 2019 on patients of stable chronic obstructivepulmonarydisease. A totalnumber of 100 patients were enrolled for the study but 20 patients, 10 from each group lost their follow up.

In this study, the total number of patients who completed the study were 40 in each group. Out of 40 patients, 28 were males and 12 were females (Table 1).

Patients who were following the General Medicine department (SKIMS) with following inclusion criteria were taken for study.

1. Previous diagnosis of COPD based on American thoracic society definition
2. Onset of respiratory difficulty after the age of 30 yrs.
3. Respiratory symptom (Dyspnea, cough and sputum production)) for greater than 5 years.
4. Patients without an exacerbation of COPD.
5. No known allergy or history of Asthma (Personal or family)
6. No overt evidence of cardiac decompensation.
7. No steroid treatment for at least one month before entrance into the study.

To see the effect of steroids on pulmonary function tests and Arterial blood gases, patients were divided into case and control group.

- Patients in case group were gives prednisolone 30 mg orally for two week (tapering dose).
- Patients in control group were given placebo for the same duration of two weeks. Steroid response was defined as 15% improvement in baseline FEV.

Statistical Analysis: The characteristics of all treatment groups were compared for both demographic and efficacy variables. Data were expressed as mean ± standard error mean (SEM). The values of symptom score for each group were anlysed by analysis of variance (ANOVA) followed by Turkey`s test.Comparison was made between baseline and post treatment after two weeks between treatment groups. $p<0.05$ considered as significant.

OBSERVATION AND RESULTS

This study was done in the department of General Medicine (SKIMS) from August 2017 to January 2019 on patients of stable chronic obstructive puImonarydisease. A total number of 100 patients were enrolled for the study, but 20 patients, 10 from control and 10 from case group lost their follow up.
In this study, the total number of patients who completed the study were 40 in each group. Out of 40 patients, 28 were males and 12 were females (Table 1).

The mean age was 62.93 years (range 52-80) in case groupand 62.98 years (52-75) in control group. However, the age of the two groups was comparable ($p>0.05$)(Table 1).

In this study we found bilateral rhonchi on chest auscultation as the commonest clinical sign, which was present in 85% of patients from case group and 92.59% of patients from control group.

Cyanosis was present in 15% of patients in case group and 17.5% of patients in control group. Loud P2 suggestive of pulmonary arterial hypertension was present in 15% of patients in case group and 59% of patients from control roup (Table 2)
The chest radiographic evidence of hyper inflated lung fields, suggestive of chronic obstructivepulmonary disease was present in 82.5% of patients in both case and control group (Table 2).

The most common electrographic finding in both group was Ppulmonale suggestive of right atrial hypertrophy (Table3)The biochemical parameters were within the normal range in both case and control group (Table.4)

The mean hemoglobin in case group was 15.33 gm% and 15.24 gm% in control group. The mean haematocrit in case group was 48.97 and 49.07 in the control group (Table 5). The pulmonary function tests (FEV, FVC, FEV FVC) in both groups were comparable before giving steroids or placebo (Table 6).

The pulmonary function tests (FEV, FVC, FEV,/FVC and %age change in FEV, FVC, FEV /FVC) were comparable in case and control group after giving steroids and placebo respectively. The maximum %age change in FEV,/FVC was not more than 7% in case group (Table 7). The arterial blood gases in both case and control groups were comparable before giving steroids or placebo respectively (Table 8).

The arterial blood gases in both case and control groups were comparable after giving steroids and placebo respectively (Table 9).The adverse effects consequent to steroid therapy in case group were hypertension, ulcer symptoms and hyperglycemia (Table 10).

Table 1 Showing demographic profile, duration of smoking and symptom duration of case and control group.

Parameter	Case Group (n=40)	Control Group (N=40)	Statistical Significance
Age (in Years) Mean±SD	62.93±5.17	62.98±5.49	P>0.05
Sex Male	28(70%)	28(70%)	P>0.05
Female	12(13%)	12(13%)	P>0.05
Duration of smoking (In years (Mean±SD)	14.25±14.96	17.95±14.05	P>0.05
Duration of Symptoms (In years (Mean±SD)	9.85±3.66	8.98±3.13	P>0.05

The Age, Sex, duration of smoking and symptoms of case and control group were comparable (P>0.05).

Table 2 Showing Clinical Signs of case and control group.

Parameter	Case Group (n=40)	Control Group (N=40)	Statistical Inference
Cyanosis (%)	6(15%)	7(17.5%)	P>0.05
Pedal edema (%)	14(35%)	14(35%)	P>0.05
Rhonchi (%)	14.25±14.96	17.95±14.05	P>0.05
Loud P2 (%)	6(15%)	2(5%)	P>0.05
Hepatomegaly (%)	5(12.5%)	3(7.7%)	P>0.05

The clinical signs, Cyanosis Pedal edema, Rhonchi, Loud P2 and Hepatomegaly of case and control group were comparable (p>0.05)

Table 3 Showing Radiographic and Electrocardiographic parameters of case and control group.

Parameter	Case Group (n=40)	Control Group (N=40)	Statistical Inference
CXR Hyperinflated Lung fields (%)	33(82.5%)	32(82.5%)	P>0.05
P.Pulmonale (%)	11(27.5%)	13(32.5%)	P>0.05
RAD (%)	3(7.5%)	3(7.5%)	P>0.05

CXD- chest x-ray, RAD – Right axis deviation

As is evident from table 3, the radiographic and electrocardiographic parameter of case and control were comparable (p>0.05)

Table 4 Showing Biochemical parameters of case and control group

Parameter	Case Group (n=40)Mean±SD	Control Group(N=40)Mean±SD	Statistical Inference
Sr. bilirubin	0.99±.46	1.12±.48	P>0.05
SGOT	30.87±6.43	32.90±10.2546	P>0.05
SGPT	32.02±7.68	32.82±13.08	P>0.05
Sr. Albumin	3.44±0.32	3.30±0.29	P>0.05
Bl. Sugar	85.67±11.40	86.26±15.09	P>0.05
Bl. Urea	43.33±25.98	47.63±36.71	P>0.05
Sr. Creatinine	1.23±0.57	1.30±0.64	P>0.05

SGOT- Serum glutamate oxalocactate transaminase; SGPT – Serum glutamate pyruvate transaminase. The Biochemical parameter (Sr. bilirubin, SGOT, SGPT, Sr. Albumin, BI.Sugar, BI. Urea, Sr. Creatinine) in the case and control group are comparable (p>0.05).

Table 5 Showing Hematological parameters of case and control group.

Parameter	Case Group (n=40) Mean±SD	Control Group (N=40) Mean±SD	Statistical Inference
Hb in gm%	15.33±1.01	15.24±1.20	P>0.05
TCL	7.61±2.61	6.71±1.93	P>0.05
Polymorphs (%)	70.12±8.95	66.88±1.93	P>0.05
Lmphocytes (%)	21.23±7.63	23.80±7.48	P>0.05
Monocytes (%)	4.50±2.75	4.85±2.74	P>0.05
Haematocrit (%)	48.97±3.15	49.07±3.01	P>0.05

Hb – Haemoglobin; TLC – Total leucocyte count

Hematological parameters of case and control group were comparable (P>0.05)

Table 6 Showing Pulmonary function tests of case and control group before steroids and placebo respectively

Parameter	Case Group (n=40)	Control Group (N=40)	Statistical Inference
FEV_1 (In Liters) Mean±SD	1.720±0.22	1.74±0.24	P>0.05
FVC (In Liters) Mean±SD	2.85±14.96	2.87±0.31	P>0.05
Fev_1/ FVC (Mean±SD)	59.45±4.36	59.72±3.99	P>0.05

FeV_1= forced expiratomy volume in Ist second, FVC – FCV – Forced vital capacity

Pulmonary function tests of case and control group before steroids and placebo respectively were comparable (P>0.05)

Table 7 Showing Pulmonary function tests of case and control group before steroids and placebo respectively

Parameter	Case Group (n=40) Mean±SD	Control Group (N=40) Mean±SD	Statistical Inference
FEV1 (In Liters)	1.76+0/184	1.76+0.215	P>0.05
FVC (in Liters)	3.44+4.26	2.81+4.36	P>0.05
FEV1 / FVC	60.07+3.53	59.93+4014	P>0.05
(%) age change in FEV1	3.21+7.52	1.38+6.47	P>0.05
(%) age change in FVC	3.16±3.63	2.38±2.73	P>0.05
(%) age change in FEV1/FVC	0.98±5.98	0.39±4.92	P>0.05

FEV1 = Forced expiratory volume in Ist second, FVC – Forced vital capacity; % age percentage

Pulmonary function tests of case and control group after steroids and placebo respectively were comparable (P>0.05)

Table 8 Showing arterial blood gas analysis of case and control group before steroids and placebo respectively

Parameter	Case Group (n=40) Mean±SD	Control Group (N=40) Mean±SD	Statistical Inference
pH	7.38±1.79	7.32±.47	P>0.05
PO_2 in mmHg	63.05±3.05	63.28±3.15	P>0.05
PCO_2 in mm Hg	46.50±2.72	46.38±1.35	P>0.05
O_2 Sat (%)	90.90±1.86	92.18±1.50	P>0.05

Arterial blood gas analysis of case and control after steroids and placebo respectively were comparable (P >0.05)

Table 9 Showing arterial blood gas analysis of case and control group after steroids and placebo respectively

Parameter	Case Group (n=40) Mean±SD	Control Group (N=40) Mean±SD	Statistical Inference
pH	7.40±1.08	7.40±1.22	P>0.05
PO_2 in mmHg	65.83±3.57	64.33±2.88	P>0.05
PCO_2 in mm Hg	44.7±1.83	45.93±1.39	P>0.05
O_2 Sat (%)	91.30±14.27	93.93±1.39	P>0.05
% age change in pH	.44±1.11	.49±1.57	P>0.05
(%) age change in PO_2	3.93±4.61	3.49±1.25	P>0.05
(%) age change in PCO_2	-3.21±4.72	-1.53±2.88	P>0.05
(%) age change in $SatO_2$	2.48±2.36	1.90±1.82	P>0.05

Arterial blood gas analysis and % age change of case and control group after steroids and placebo respectively were comparable (p>0.05)

Table 10 Showing steroids induced adverse effects in case group

S.No.	Adverese effect	No. of Patients
1.	Hypertension	12
2.	Peptic ulcer symptoms	8
3.	Hyperglycemia	4

DISCUSSION

This study was conducted in the department of General Medicine (SKIMS) on patients of stable chronic obstructive pulmonary disease. By stable, we meant a patient of chronic obstructive pulmonary disease documented by spirometry, who were on regular follow up without an acute exacerbation. The total number of patients who completed the study were 40

in case group and 40 in control group. In case group patients were put on prednisolone 30 mg once a day for a period of 14 days Pulmonaryfunction tests and arterial blood analysis were performed before and after receiving the tapering dose of prednisolone for two weeks. In control group same number of patients were given placebo for a period of two weeks and response was monitored by same tests as in case group.

In our study 80% of patients were smokers in each group with mean smoking duration of 14.25 years in case group and 17.95 years in control group. Among 32 male patients, 28 were smokers and among 12 female patients, 4 were smokers in each group. So, smoking appeared to be major risk factor for chronic obstructive pulmonary disease. A study conducted by Francis C. Lowell *et al* [11] in 1956 concluded that chronic obstructive disease is a disease of smokers. Also in the study conducted by WKC Morgan *et al* in 1964, all the patients were heavy smokers. Therefore, in our study it appeared that althoughsmoking is a major risk factor for chronic obstructive pulmonary disease but other factors like environmental pollution also plays a role.

In our study none of 40 patients treated with prednisolone (30 mg tapering dose for 14 days) had increase in FEV1/FVC by> 15% to qualify for response.

The maximum response was not > 7% increase in FEV1/FVC. This response was comparable to patients in control group where placebo was given for the same duration(p-0.05) However, it was observed that>50% patients in case group noticed subjective improvement in their symptoms probably because of the euphoriant effect of steroids. This is in agreement with the study conducted by James H. Cullen andWilliam U. Reidt[22] who concluded that half of the patients noted subjective improvement while receiving steroids but none showed any significant change in pulmonary function tests. This study thus suggested that long term steroid therapy is not justified in chronic pulmonary disease.

In our study the most noticeable feature was the development of steroid related side effects in case group. More than 60% of patients developed adverse effects, when they were followed for about I monthafter completing 14 days course of steroids. The most common n adverse effect was hypertension followed by peptic ulcer symptoms and hyperglycemia. However, none of the patients developed gastrointestinal bleeding or hyperglycemia severe enough to warrant treatment. In previous studies hyperglycemia was observed as major adverse effect.

In our study, the change in pulmonary function tests and arterial blood gases in case and control group were comparable (p-0.05), so the of steroids to relieve the obstruction in patients with chronic obstructive pulmonary disease has not been found to be of value. This is in agreement with most of studies conducted on patients of COPD without exacerbation.

SUMMARY & CONCLUSION

Steroid response was defined as 15% increase in FEV1/FVC after receiving tapering dose of prednisone 30 mg for 2 weeks.None of patients in case group showed increase in FEV1/FVC of 15%. The change in pulmonary function tests and arterial blood gases were comparable in each group (p>.0.5).So steroids in stable patients of COPD, are best to be avoided.

The major limitations in use of steroids in stable COPD patients was development of steroid related adverse effects. Smoking appearedto be the major risk factor for COPD.

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