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Original Research Article

A Study to Evaluate Hypercoagulable State in Patients of Chronic Obstructive Pulmonary Disease

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Abstract

COPD is a multisystem disorder associated with pulmonary and systemic inflammation. This systemic inflammation contributes to various extra pulmonary manifestations of COPD. Exacerbations are associated with increased airways inflammation. In this study we studied prothrombotic state in COPD patients by analysing fibrinogen and D dimer levels.

Aims and Objectives: To study the prothrombotic markers plasma D-dimer and fibrinogen levels in stable COPD patients and during exacerbation and to compare the above parameters during exacerbations of COPD on day 1 and after stabilization, and its significance if any.

Material and Method: 30 patients with COPD exacerbation were studied. Blood samples were obtained for fibrinogen and D-dimer levels on two different occasion-on day 1 of admission and at follow up when clinically stable after day 5 in exacerbation group and on entry of study in stable COPD group. Data were compared in both groups. Statistical testing was conducted with the statistical package for the social science system version SPSS 17.0.

Result: Most patients fall into the age group 41-70 year corresponding to the peak age group of COPD population. The sex distribution is study is 47 were male (78%) and 13 female (22%). All patients were smoker. The smoking mean was found to be 25±5.9 pack years. , the mean value of fibrinogen in COPD exacerbation group was 491±225mg% which declined to 267±89mg% after stabilization. In stable COPD group, the mean value of fibrinogen was 426.86±144.0mg%. In conclusion, we have demonstrated in the study the presence of a hypercoagulable state in COPD patients. However, the present study has the limitation of small sample size. Further studies are needed to identify the exact mechanisms underlying the hypercoagulative state in COPD, and to determine whether anticoagulant therapy is clinically useful in COPD.

Keywords: COPD, hypercoagulable state, fibrinogen, D-dimer.

Introduction

COPD is a common disorder of significant mortality and morbidity [1].COPD is a multisystem disorder [2] associated with pulmonary and systemic inflammation . This systemic inflammation contributes to various extra pulmonary manifestations of COPD. [3] An exacerbation of COPD is defined as an event in the natural course of the disease characterized by a change in the patient's baselines dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD. Exacerbations are associated with increased airways inflammation. A state of hypercoagulabilty resulting from inflammatory activation of endothelium may well occur during COPD exacerbation and could be a significant causative factor for pulmonary thromboembolism. Fibrinogen is a marker of inflammation and D-dimer is a marker of secondary fibrinolysis following thrombosis. These parameters may be used for evaluation of procoagulant state in COPD. We studied the existence of a prothombotic state, by analysing fibrinogen and D-dimer levels in stable COPD patients and during acute exacerbation

Aims and Objectives

1. To study the prothrombotic markers plasma D-dimer and fibrinogen levels in stable COPD patients and during exacerbations.
2. To compare the above parameters during exacerbations of COPD,on day 1 and after stabilization , and its significance if any.

Materials and Methods

Study Population-It is an observational cross sectional study conducted at Department of Pulmonary Medicine, Fortis Hospital,Vasant Kunj New Delhi. 30 consecutive patients admitted to hospital with exacerbation of COPD and 30 stable patients from outpatient department after obtaining informed consent were included in the study. The diagnosis of COPD was made according to GOLD criteria.

Inclusion Criteria

1. Patients of stable COPD
2. Patients of acute exacerbations of COPD

A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and a history of exposure to risk factors for the disease. Spirometry is required to make the diagnosis; the presence of a post-bronchodilator $FEV_1/FVC < 0.70$ confirms the presence of persistent airflow limitation and thus of COPD. Patients who presented to opd without exacerbation was designated as stable COPD.

Exclusion Criteria

1. Chronic diseases with acquired thrombotic risk factors like diabetes, hypertension, coronary artery disease, chronic kidney disease, chronic liver, malignancy and sepsis.
2. Immunocompromised conditions.
3. Patients on anticoagulant therapy, statins or anti-hypertensive drugs

Study Design- 30 patients with exacerbation were admitted. After obtaining detailed history and physical examination, Blood investigation including hemogram, kidney function test, liver function test, arterial blood gas analysis were done. Chest x-ray was also done. Spirometry was done for documentation of FEV1, FVC and FEV_1/ FVC values. All the patients were prescribed a standardized treatment regimen. They were discharged after minimum of 5 days of inpatient care. Medication history was taken for identifying exacerbation and to exclude if the patients were on anticoagulants,or statins or antihypertensives ,as these medicines will alter the results . History of smoking was taken. Detailed past history

was taken regarding any malignancy, sepsis, coronary artery disease ,Diabetes ,hypertension ; as these prothrombotic states per se ,so our results will be altered. Chronic kidney disease and chronic liver disease was also excluded. Blood samples were obtained for fibrinogen and D-dimer levels on two different occasion-on day 1 of admission and at follow up when clinically stable after day 5 in exacerbation group and on entry of study in stable COPD group.

Statistical Analysis- Statistical testing was conducted with the statistical package for the social science system version SPSS 17.0.Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute numbers and percentage. Data were checked for normality before statistical analysis. Normally distributed continuous variables were compared using the unpaired t test, whereas the Mann-Whitney U test was used for those variables that were not normally distributed.. Nominal categorical data between the groups were compared using Chi-squared test or Fisher's exact test as appropriate. $P<0.05$ was considered statistically significant.

Results And Observation

Following are the results in our study.

Demographic Characteristics of the Patients (Descriptive Analysis)

Age distribution -The age distribution of patients as follows.Three patients (5%) fall into less than 40 years, 18 patients (30%) in 41-50 years, 17 patients (28.3%) in 51-60 years, 15 patients (25%) in 61-70 years and 7 patients (11.7%) in > 70 year age group. Most patients fall into the age group 41-70 year corresponding to the peak group of COPD population.

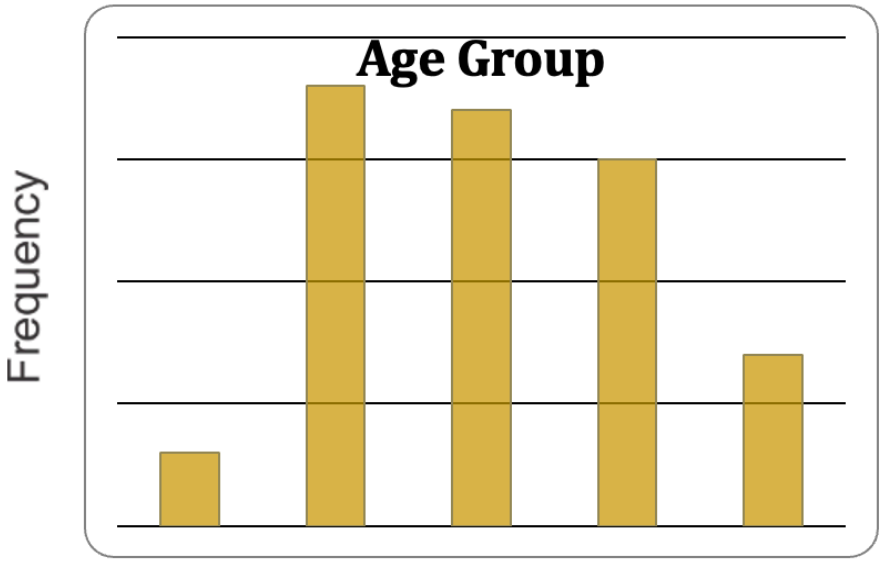

Figure1: Distribution of all study subjects according to different age groups

- Table 1 shows distribution of patients according to stable COPD and exacerbation control group. This shows almost similar frequency of different age groups between stable COPD and exacerbation group(p-value=0.434)

Table 1: Age distribution of patients according to stable COPD group and exacerbation group

Age Groups	Study Group				P Value
	Stable COPD Group		Exacerbation Group		
	Frequency	%	Frequency	%	
<=40 yrs	3	10.0%	0	0.0%	0.434
41 - 50 yrs	9	30.0%	9	30.0%	
51 - 60 yrs	8	26.7%	9	30.0%	
61 - 70 yrs	6	20.0%	9	30.0%	
> 70 yrs	4	13.3%	3	10.0%	
Total	30	100%	30	100%	

Sex Distribution

- 47 (78.3%) were male and 13(21.7%) female.

Distribution of the patients depending upon smoking.

- All the patients were smokers.

Distribution of patients according to **GOLD Criteria**

- In stable COPD group 4 patients(6.7%) were GOLD stage II (Moderate), 30(50%) GOLD stage III (Severe), 26 (43.3) GOLD stage IV (very severe).while in COPD exacerbation group 15 (50%) were severe and 15 patients(50%)were very severe,

Clinical characteristics of patients with COPD exacerbation at entry to the Study

- All patients were smoker with a smoking mean of 25±5.9 pack years. The mean value of PaO_2 was 59.39±18.73 mm of Hg and $PaCO_2$was 54.75±12.30 mm of Hg. The mean values of other blood investigations and arterial blood gas parameters are shown in the table 13.

Table 2: **Demographic & Biochemical Characteristics of Patients at the Baseline (During Exacerbation State) (N=30)**

Characteristics	Value (±SD)
Age	60.2±11.29
Sex (M/F)	23/7
BMI	26.4±1.77
Pack Years	25±4.9
Biochemical Parameters	
Hemoglobin (g/dl)	13.59±1.96
TLC	13748.3±3506.63
Urea	36.56±23.66
Creatinine	0.94±0.64
pH	7.36±0.66
pO2	59.39±18.73
PaCO2	54.75±12.30
So2	84.28±16.24
HCO3	29.14±4.67

Data are presented mean±SD; PaO2: partial pressure of oxygen in arterial blood, PaCO2 partial pressure of carbon dioxide in arterial, mmHg millimetres of mercury.

Pulmonary Function Parameters after stabilization –mean FEV1 % is33±10.95 , FVC(L) is 0.560 ± 0.148 and FEV1/FVC is 57.33±7.11

Analysis of prothrombotic markers

D-dimer was obtained either as positive or negative value. However, fibrinogen was obtained as quantitative values. For D-dimer, in COPD exacerbation group, 20 had negative and 10 had positive, of which only 2 patients remain positive on follow up after minimum of 5 days of inpatient stabilization. Of the stable COPD group enrolled from outpatient departments, 5 had positive result. In COPD exacerbation group, the mean value of fibrinogen was 491.09 ± 225.56mg%,

Characteristics of the patients during stable COPD phase

Table 3: **Clinical characteristics of the patients during stable COPD phase (n=30)**

Characteristics	Mean±SD
Age	56.13±11.89
FEVI% Predicted	37.83±13.58
FEVI/FVC%	60.96±6.68
FVC(L)	0.623 ± 0.221
Fibrinogen	426.86±144.0

Value of d-dimer in stable COPD group (n=30)- d dimer is positibe in 5 and negative in 25 patients.

Comparison of prothrombotic parameters-

The prothrombotic markers were compared using analysis of variance (ANNOVA) between COPD exacerbation, post stabilization and stable COPD group. P-value <0.05 was considered significant.

Comparison between COPD exacerbation and post stabilization-

The mean values of prothrombotic markers of patients with COPD exacerbation was compared with their value after exacerbation has subsided i.e. after day5(minimum). The values of D-Dimer and fibrinogen were observed to be raised significantly as compared to their values stabilization. This is in agreement with our hypothesis that COPD exacerbation is a prothrombotic state.

Table 4: Changes in coagulation parameters in COPD patients (comparison between exacerbation and post stabilization)

Prothombotic Markers	COPD exacerbation	Post stabilization (CI 95%)	p-value
Fibrinogen	491.09(406.86-573.31)	267.45(233.93-300.97)	<0.001*

Table 5: Changes in D-dimer in COPD patients (comparison between exacerbation and post stabilization)

D-Dimer	Exacerbation		Post stabilization		p value
Negative (0)	20	66.7%	28	93.3%	0.021
Positive(1)	10	33.3%	2	6.7%	

Comparison between COPD exacerbation and stable COPD-

The values of prothrombotic markers D-Dimer and fibrinogen were compared between COPD exacerbation and stable COPD patient enrolled from out patient department. There was no significant difference in exacerbation of COPD as compared to stable COPD patients. However the mean values of fibrinogen even in patients of stable COPD are much more raised than their normal reference range.

Table 6: Comparison of D-dimer in stable COPD patients and exacerbation group

d-dimer	Study Group				P Value
	Stable COPD Group		Exacerbation Group		
	Frequency	%	Frequency	%	
Negative (0)	25	83.3%	20	66.7%	0.136
Positive (1)	5	16.7%	10	33.3%	

Table 7: Comparison of fibrinogen in stable COPD patients and exacerbation group

	Study Group						P Value
	Stable COPD (n=30)			Exacerbation Group (n=30)			
	Mean ± SD	Median	Min - Max	Mean ± SD	Median	Min - Max	
Fibrogen	426.86 ± 144.00	388.65	177.2 - 741.6	491.09 ± 225.56	434.40	148.0 - 1056.0	0.344

Comparison between COPD post stabilization and stable COPD patients

Prothrombotic markers were compared between stable COPD enrolled from out patient department and the mean values of these parameters in COPD exacerbation patients after the exacerbation subsided. A significant difference was seen in the mean values of fibrinogen levels as shown in the table below.

Table 8: Changes in coagulation parameters in COPD patients (Comparison between post stabilization and stable COPD patients)

Prothombotic Markers	Stable COPD	Post stabilization (CI 95%)	p-value
Fibrinogen	426.86(373.08-480.63)	267.45(233.93-300.97)	<0.001*

* P<0.05 compared with patients with COPD exacerbation

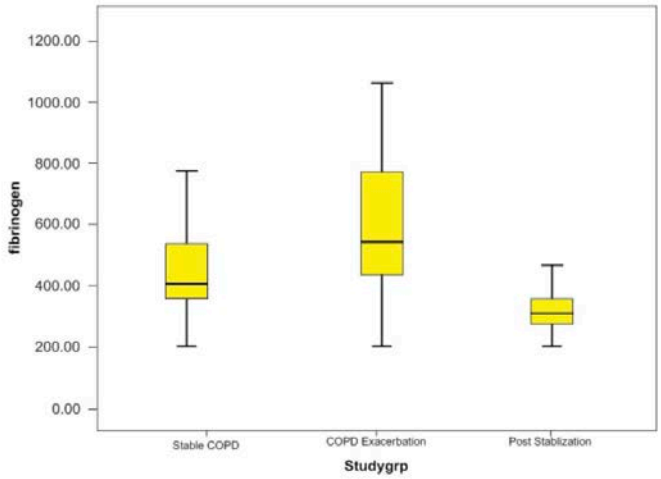

Figure 2: **Box Whisker plot showing comparison of fibrinogen among different groups**

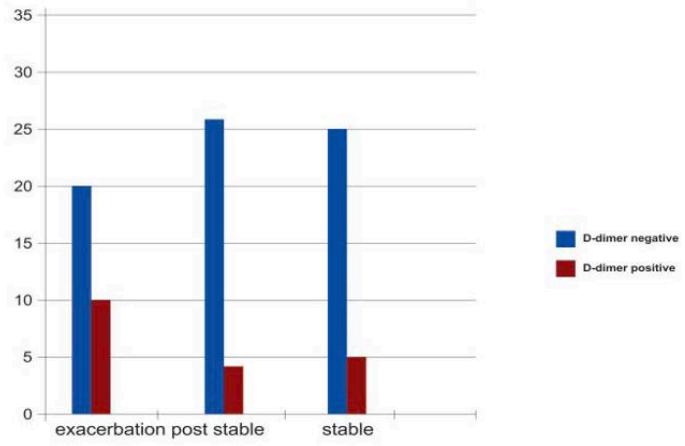

Figure 3 : value of D-dimer in different groups

Analysis of correlations:-

Correlation analyses was done between prothrombotic markers and partial pressure of arterial oxygen and carbon dioxide, GOLD stage of COPD and FEVI using Spearman's Rank correlation test in patients presenting with acute exacerbation.

Discussion

The present study was done to study the prothrombotic state is COPD acute exacerbation. Thirty patients who were admitted to hospital with exacerbation of COPD and 30 stable patients from outpatient department after obtaining informed consent were included in the study.. Most patients fall into the age group 41-70 year corresponding to the peak age group of COPD population. The sex distribution is study is 47 were male (78%) and 13 female (22%).

In the present study, the mean value of fibrinogen in COPD exacerbation group was 491±225mg% which declined to 267±89mg% after stabilization. In stable COPD group, the mean value of fibrinogen was 426.86±144.0mg%.

The mean values of fibrinogen levels in COPD exacerbation group was significantly higher than post stabilization ($p<0.001$). It is also higher in stable COPD as compared to post stabilization ($p<0.001$). In a study Mehmet and associates [4] showed fibrinogen levels as markers of COPD exacerbation. The mean levels of fibrinogen were 447.67±128%, 346.88±92.3% and 289.99±39.9 in COPD exacerbation, stable COPD and control group. The levels of fibrinogen in COPD exacerbation group was higher than stable COPD group ($p=0.001$) and control ($p<0.001$).

Ya-jun Song and coworkers [5] demonstrated fibrinogen levels are much raised in elderly patients with COPD exacerbation combined with respiratory failure than without respiratory failure. The mean value of fibrinogen in the study group was 440±64mg% and in control group was 320±64mg%, the difference being significant ($p<0.01$). Our study also showed similar result. In our study level of fibrinogen was found to be more than their normal range in both stable COPD and during exacerbation but the difference was not statistically significant. Although after treatment and stabilization of exacerbation the difference is statistically significant.

In the study of Ya-jun Song and coworkers [5], plasma D-dimer was significantly elevated in elderly COPD patients with exacerbation and respiratory failure (0.036±0.026) as compared to patients of exacerbation without respiratory failure (0.011±0.008). In our study, D-dimer was measured qualitatively. In the exacerbation group, 10 patients had positive D-dimer test which declined to 2 patients in post

stabilization phase (p=0.008). In the stable COPD group 5 patients had positive D-dimer value. So the difference in both stable COPD and during exacerbation but the was not statistically significant. Although after treatment and stabilization of exacerbation the difference is statistically significant.

This study provides evidence that a pro-thrombotic condition is associated with acute exacerbation of COPD. The markers of prothrombotic state; fibrinogen, D-dimer were significantly raised in acute exacerbation which subsequently decreased on stabilization. The systemic inflammation during COPD exacerbation may be the cause of the prothrombotic state. However these markers were also raised significantly in stable COPD patient as compared to post stabilization value. This discrepancy might be attributable to intravenous steroid therapy decreasing the systemic inflammation. Similarly in the stable COPD patients the systemic inflammation is ongoing, hence these markers had higher value.

The clinical implication of elevated, D-dimer and fibrinogen concentrations in the blood during acute exacerbation of COPD is that this condition might increase the likelihood of thromboembolic events in these patients just as it has been reported ischemic heart disease [6,7]. Death from PTE occurs in about 10% of patients admitted for an acute exacerbation of COPD [8].

Numerous studies report incidences of acute VTEs as high as 31% during admission for exacerbation of COPD [9,10,11]. However, the prevalence of PTE was questioned when in a recent study only 6.2% of suspected and 1.3% of unsuspected patients who attended the emergency department for an exacerbation of COPD were diagnosed as having PTE [12]. Concerns were raised of the prior studies having a selection bias of patients. Suggestions have been raised that prolonged and complicated hospital stays may have higher incidences of VTEs and that patients having re-admissions secondary to further exacerbation recurrences may be attributed to PTE. [13]

The heightened clotting state during COPD exacerbation may predispose to venous thromboembolism (as in acute ischemic heart disease) and could, in principle, justify a general recommendation for anticoagulation and pharmacological thromboprophylaxis in these patients during exacerbation of their disease.

Diagnosis of concomitant PE in these patients is often missed because symptoms of acute exacerbations of COPD may mimic PE, additionally markers of hypercoagulability are also increased ,making the differentiation more difficult. So high index of suspicion for PE should be there.

In conclusion, we have demonstrated in the study the presence of a hypercoagulable state in COPD patients. However, the present study has the limitation of small sample size. Further studies are needed to identify the exact mechanisms underlying the hypercoagulative state in COPD, and to determine whether anticoagulant therapy is clinically useful in COPD.

Conclusion

Fibrinogen level is significantly elevated during COPD exacerbation state which decreased after stabilization. D-dimer also found to be increased during COPD exacerbation which also normalizes after stabilization. COPD exacerbation is a state of heightened hypercoagulablility. In addition, Fibrinogen levels are higher than normal in stable copd patients also. It implies baseline inflammation is also ongoing in stable COPD. Fibrinogen levels correlates with FEV1, GOLD stage and PaCO2, so it can be used independently as a marker of COPD severity. The heightened clotting state may predispose to venous thromboembolism (as in acute ischemic heart disease). Furthermore the symptoms of pulmonary embolism and AECOPD mimic each other. These could, in principle,

justify a general recommendation for anticoagulation and pharmacological thromboprophylaxis in these patients during exacerbation of their disease and thorough evaluation of thromboembolism.

Limitation-It is single hospital based study and sample size is less.

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