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ORIGINAL RESEARCH

To Study Association Between the Levels of Oxidative Stress Markers and Pulmonary Hypertension in Patients with Chronic Obstructive Pulmonary Disease at a Tertiary Care Hospital

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ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) is a disease state characterized by airflow limitation that is not fully reversible. An increased inflammatory response in the lungs plays a central role in the pathogenesis of COPD. Oxidative stress and systemic inflammation are co-dependent processes. Pulmonary hypertension is a common complication of chronic obstructive pulmonary disease (COPD). The present study is an attempt to study the various markers of oxidative stress in COPD and their co relation with pulmonary hypertensionusing 2D ECHO findings.

Materials and Methods: The present study enrolled 100 participants, 50 of them diagnosed cases of COPD and the remaining 50 as control. Apart from the chest X ray, routine blood investigations, sputum AFB examination and PFT, 6-minute walk test (6MWT), 2D Echo and levels of above mentioned oxidative and inflammatory markers were done of the patients. Pulmonary hypertension diagnosed based on the Transthoracic 2D – ECHO by TR jet method – presence of mPAP more than 25 mmHg considered as the criteria for defining pulmonary hypertension. As far as the quantitative data was concerned, comparison between the 2 groups was done using unpaired t test, and for the qualitative data appropriate data was used.

Results: Out of the 50 COPD patients, 34 were smokers. Majority of the smokers had a smoking index between 101 and 300. Only 3 patients had a smoking index of more than 500.41 patients in the study group had normal pulmonary arterial pressure. Only 4 of them had mild pulmonary hypertension, whereas 5 had moderate pulmonary hypertension. None of the patients had severe pulmonary hypertension. All the patients in the control group had normal pulmonary arterial pressure. The mean pulmonary hypertension in the study group was 29.36 mm Hg, whereas it was 24.98 mm Hg in the

control group. It was found that the study group had a higher level of these biomarkers as compared to the control group. None of the biomarkers had a significant association with pulmonary hypertension.

Conclusion: This study may pave way for therapeutic rationale in COPD by concentrating on the main pathophysiology of COPD, which is underlying oxidative stress and inflammation as it was found that the study group had a higher level of these biomarkers as compared to the control group. None of the biomarkers had a significant association with pulmonary hypertension indicating that hypoxia rather than oxidative stress plays a major role in development of pulmonary hypertension in COPD patients.

Keywords: COPD; Pulmonary Arterial Pressure; Oxidative Stress; Inflammation.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disease state characterized by airflow limitation that is not fully reversible. The airflow obstruction is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles and gas.[1]

Oxidative stress and systemic inflammation are co-dependent processes. Oxidative stress result in the release of chemotactic factors, such as IL-8 from airway epithelial cells[2]and epithelial cells from COPD patients have been shown to release more IL-8 than those of smokers or healthy persons.[3] An increased inflammatory response in the lungs plays a central role in the pathogenesis of COPD.[4,5] Oxidative stress may cause and exacerbate this inflammation through the increased production of redox-sensitive transcription factors, such as Nuclear factor kappa-B (NF-κB) and activator protein -1 (AP-1), and also by activation of the extracellular signal-regulated kinase, C-JUN *N*-terminal kinase, and p38 mitogen-activated protein kinase pathways.[6,7]

Pulmonary hypertension is a common complication of chronic obstructive pulmonary disease (COPD).Pulmonary hypertension is defined as a mean pulmonary artery pressure of more than 25 mmHg at rest or 30 mmHg with exercise.[8]The present study is an attempt to study the various markers of oxidative stress in COPD and their co relation with pulmonary hypertensionusing 2D ECHO findings.

MATERIALS AND METHODS

The presentsingle centric observational open labelled case control study enrolled 100 participants, 50 of them diagnosed cases of COPD and the remaining 50 as control was conducted in Department of Pulmonary Medicine, Grant Government Medical College and Sir JJ Group of Hospitals, Mumbai, in collaboration with the Department of Biochemistry after taking permission from the Institutional Ethics Committee.

Inclusion criteria consisted of patients above the age of 18 years of either gender, patients willing to be enrolled in the study and patients diagnosed as a case of COPD, as per GOLD Guidelines.

Exclusion criteria consisted of patients with underlying life-threatening diseases like myocardial infarction or stroke, patients having some other underlyingdisease which may influence the oxidative stress markers, sputum positive pulmonary tuberculosis, patients who are unable to perform PFT, patients unable to perform 6 minute walk test, pregnant/lactating mothers and patients not willing to be enrolled in the study.

Patients complaining of breathlessness, cough or sputum production and /or history of exposure to risk factors were chosen from patients attending OPD or referred from other departments at the tertiary care center. Spirometry was done and diagnosis of COPD is confirmed on the basis of GOLD criteria. The patient's age, height and weight (without shoes) were recorded for calculation of reference values.Age was expressed in years; weight

was recorded in kilograms. Height was recorded by stadiometer in centimeters and Body Mass Index(BMI) was calculated as kg/m^2.Patient's occupation was recorded to rule out exposure to smoke, fume, allergens and other particulate matter including occupation specific exposures such as silica and asbestos.Patient was asked for symptoms of breathlessness, cough, chest pain, other respiratory complaints and symptoms other than respiratory symptoms. Patient was enquired for history of recurrent rhinitis, urticaria, photosensitivity, skin rashes to rule out bronchial asthma and allergic disorder.

Patient was asked regarding history of smoking, exposure to wood / biomass smoke, past history of tuberculosis, history of diabetes, hypertension, allergy, retroviral disease. Any history of infection in childhood i.e., pneumonia, measles was asked for. Any significant drug history or history of alcoholism was asked.Relevant family history was inquired into i.e. bronchial asthma, Tuberculosis, Connective tissue disorders,etc.

Patients complaining of cough with or without sputum production, breathlessness and / or history of exposure to smoke or environmental pollutants were screened with chest X- ray, sputum AFB examination and spirometry.A written, valid, informed consent was taken from all the patients included in the study.Apart from the chest X ray, routine blood investigations, sputum AFB examination and PFT, 6-minute walk test (6MWT), 2D Echo and levels of above mentioned oxidative and inflammatory markers were done of the patients.Pulmonary hypertension diagnosed based on the Transthoracic 2D – ECHO by TR jet method – presence of mPAP more than 25 mmHg considered as the criteria for defining pulmonary hypertension(30 - 50 mmHg: Mild; 50 – 70 mmHg:Moderate;> 70 mmHg: severe pulmonary hypertension). Serum markers of oxidative stress and systemic inflammation were calculated in the special laboratory in the department of biochemistry, using standard quality equipments and well-trained technicians.

For statistical analysis "Graphad Instat Software Indiago California" was used. As far as the quantitative data was concerned, comparison between the 2 groups was done using unpaired t test, and for the qualitative data appropriate data was used.

RESULTS

Regarding smoking index, out of the 50 patients in the COPD group, 16 were nonsmokers, 2 had a smoking index between 1 and 100, 22 had a smoking index between 101 and 300, 7 had a smoking index between 301 and 500, and the remaining 3 had a smoking index above 500 (table 1).

Out of the 50 patients in the COPD group, 41 patients did not have any pulmonary hypertension, 5 patients had mild pulmonary hypertension, 4 patients had moderate pulmonary hypertension (table 2). None of the COPD patients had severe pulmonary hypertension. None of the patients in the control group had pulmonary hypertension.

The mean value of pulmonary hypertension in the COPD group was 29.36, whereas it was 24.98 in the control group. The p value of the difference in the mean values was <0.001, hence it was statistically significant (table 3).

The mean malondialdehyde in the COPD group was 8.1628, whereas it was 2.3812 in the control (table 4). The p value of the difference was <0.001, hence it was statistically significant. The mean nitric oxide in the COPD group was 60.5606, whereas it was 35.4774 in the control. The p value of the difference was <0.001, hence it was statistically significant. The mean serum carbonyl protein in the COPD group was 6.628, whereas it was 4.3836 in the control. The p value of the difference was <0.001, hence it was statistically significant.

Table 5 and figure 1 reveals an association of oxidative stress markers and pulmonary hypertension. The p value of the association of CRP and Pulmonary Hypertension in the COPD group was 0.08, hence was not significant. The p value of the association of IL 6 and Pulmonary Hypertension in the COPD group was 0.6, hence was not significant. The p value

of the association of TNF α and Pulmonary Hypertension in the COPD group was 0.5, hence was not significant. The p value of the association of LDH and Pulmonary Hypertension in the COPD group was 0.14, hence was not significant. The p value of the association of Cortisol and Pulmonary Hypertension in the COPD group was 0.3, hence was not significant. The p value of the association of Malondialdeyde and Pulmonary Hypertension in the COPD group was 0.1, hence was not significant. The p value of the association of Nitric oxide and Pulmonary Hypertension in the COPD group was 0.2, hence was not significant. The p value of the association of serum carbonyl protein and Pulmonary Hypertension in the COPD group was 0.6, hence was not significant.

Table 1: Distribution as per smoking index

Smoking Index	No of Pts in COPD Group
Non-Smoker	16
0-100	2
101-300	22
301-500	7
More Than 500	3

Table 2: Distribution of Pulmonary Hypertension in COPD and control group

Pulmonary HTN	COPD Group	Control	Total
Normal	41	50	91
Mild	5	0	5
Moderate	4	0	4
Severe	0	0	0
Total	50	50	

Table 3: Distribution of the mean values of Pulmonary Hypertension and BODE index in the COPD group and control

Mean	COPD Group	Control	Significance
Pulmonary HTN	29.36	24.98	<0.001

Table 4: Comparison of the mean values of oxidative stress markers in the COPD group and control

Markers	COPD	Control	P value	Significance
Malondialdehyde	8.1628	2.3812	<0.0001	Significant
Nitric Oxide	60.5606	35.4774	<0.0001	Significant
Carbonyl Proteins	6.628	4.3836	<0.0001	Significant

Table 5: Association of oxidative stress markers and pulmonary hypertension

Markers	P value	Significance
CRP	0.08	**Not Significant**
IL6	0.6	**Not Significant**
TNF α	0.5	**Not Significant**
LDH	0.14	**Not Significant**
Cortisol	0.3	**Not Significant**
Malondialdehyde	0.1	**Not Significant**
Nitric Oxide	0.2	**Not Significant**
Carbonyl Proteins	0.6	**Not Significant**

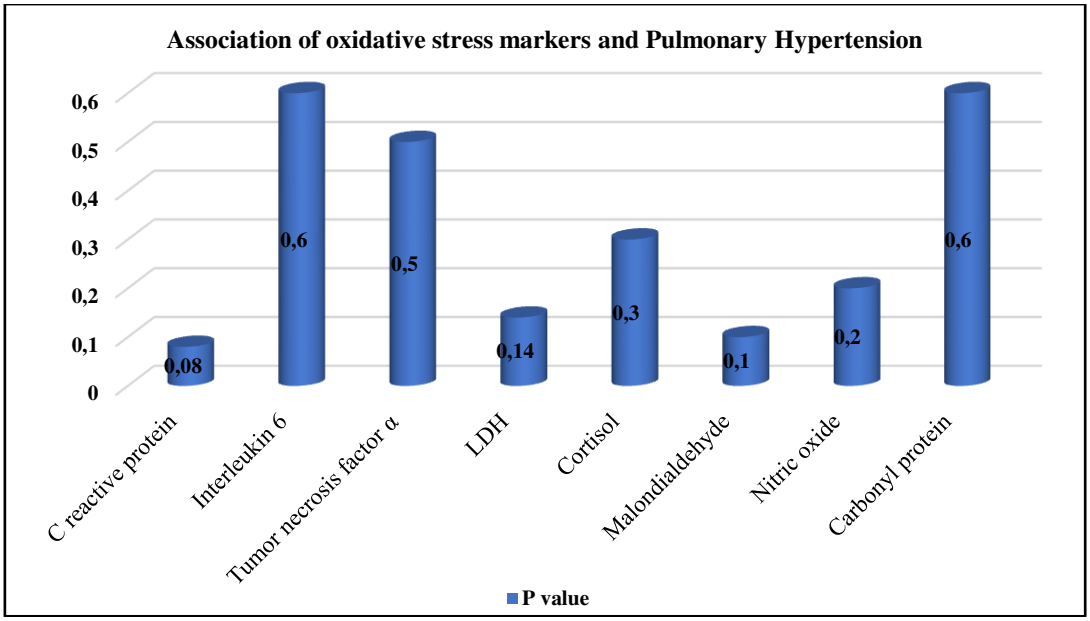

Figure 1: Association of oxidative stress markers and Pulmonary Hypertension

DISCUSSION

In our study, we tried to study whether the biomarkers had a correlation with pulmonary hypertension in the case subjects.In this study, a total of 100 patients were included, out of which 50 patients had stable COPD. The remaining 50 were healthy age and gender matched controls.

As cigarette smoking is the most important etiological factor for the development of COPD, every participant was asked in detail about their smoking status. Out of the 50 patients in the study group, 16 were nonsmokers, 2 had a smoking index between 1 and 100, 22 had a smoking index between 101 and 300, 7 had a smoking index between 301 and 500, and the remaining 3 had a smoking index above 500.

Various biomarkers for oxidative stress and inflammation were studied in the COPD patients. They were compared to the levels in the control group. The biomarkers studied were C reactive protein, interleukin 6, tumor necrosis factor α, lactate dehydrogenase, cortisol, malondialdehyde, nitric oxide and serum carbonyl proteins.

It was found out that all the biomarkers were significantly raised, by Pearson's correlation, in the study group as compared to the control group (table 4). These findings are comparable to a study conducted by WQ Gan et al, wherein he found out that individuals with chronic airflow limitation in COPD had significantly raised levels of the biomarkers.[9]

In a study conducted by Stankovic et al,[10] it was found that oxidative stress markers in COPD such as superoxide dismutase, malondialdehyde, nitric oxide, cortisol, serum carbonyl proteins were also raised.

This was also confirmed by a study conducted by Bajpai J et al[11] who evaluated serum biomarkers of oxidative stress and airway inflammation in COPD.

All the recruited patients underwent 2-dimensional echocardiography to assess the presence of pulmonary hypertension. The mean value of pulmonary hypertension in the COPD group was 29.36, whereas it was 24.98 in the control group. The pulmonary hypertension in the study group was significant when it was compared to the control (p value < 0.001).

A correlation was attempted between the biomarkers of oxidative stress and pulmonary hypertension in the study group. None of the biomarkers had a significant correlation with pulmonary hypertension in our study.

There are a few studies though which showed an association between oxidative stress markers and pulmonary hypertension. In a study carried out by Reis GS et al,[12] oxidative stress markers such as malondialdehyde were present in high levels in patients of COPD with pulmonary hypertension.
A study carried out by Fundu Aksu et al,[13] showed C reactive protein levels are increased and correlated with BODE index and pulmonary hypertension.
Similar findings were seen in a study by Pavol Joppo et al,[14] where malondialdehyde levels were raised in patients with pulmonary hypertension.
COPD is currently a concern for global mortality. The deaths due to this disease continues to soar because of the rampant use of cigarettes and because of inadequate therapy.

CONCLUSION

Current therapeutical regimen concentrate mainly on hypoxia correction and bronchodilatation, which are more or less symptomatic approach. This study may pave way for therapeutic rationale in COPD by concentrating on the main pathophysiology of COPD, which is oxidative stress and inflammation as it was found that the study group had a higher level of these biomarkers as compared to the control group. None of the biomarkers had a significant association with pulmonary hypertension thereby indicating that hypoxia rather than oxidative stress is the likely cause of pulmonary hypertension in COPD patients. As the population of patients in this study is small, the findings of this study need to be confirmed on a larger population.

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