ORIGINAL ARTICLE

STUDY THE FREQUENCY OF ANAEMIA IN PATIENTS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND ITS IMPACT ON HEALTH RELATED QUALITY OF LIFE

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ABSTRACT

Background & Objectives: Anemia is a common co-existing entity in numerous chronic diseases like COPD, but has little published evidence stating its association with this disease. The effect of COPD on the health related quality of life and mortality in COPD patients, also remains least explored. The recent studies have suggested that anemia in patients with COPD has a frequent prevalence ranging from 7.5% to 34%. This data indicate towards the necessity of knowing the real prevalence and clinical impact of Anaemia of Chronic Disease in COPD and how does it affect their Health Related Quality of Life.

Methods: This study was conducted on all consecutive stable COPD patients and related data was recorded. The St George Respiratory Questionnare (SGRQ) and the BODE index (Body Mass Index, FEV_1, Dyspnoea, Exercise Capacity) was used to analyze the Health Related Quality of Life and the morbidity level of included patients.

Results: 32 COPD patients had anaemia. The analysis showed significantly higher symptom score in the anaemic COPD patients (p=0.04). Also anaemics had significantly lesser BMI (p=0.03), significantly poor dyspnoea score (p=0.05) and significantly lesser six minute walk distance (p=0.05).

Conclusions: The prevalence of anaemia in stable COPD patients is 32%, which is significantly associated with low BMI, dyspnoea and reduced exercise capacity. These factors can affect the quality of life of COPD patients thus, leading to increased morbidity. Hence, treating anaemia should hold a special place in treatment regime for COPD.

Keywords: Anaemia of chronic disease, BODE index, Chronic Obstructive Pulmonary Disease, Health Related Quality of Life, St George Respiratory Questionnare

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an important lifestyle related chronic inflammatory pulmonary disease with major impact on the global morbidity and mortality. It is the fourth leading cause of death in the world and has been projected to become the third leading cause of death and fifth leading cause of loss of 'Disability Adjusted Life Years' (DALYs) by the year 2030.[1] COPD is defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014 update as a "common preventable and treatable disease, characterized by persistent airflow limitation that is progressive and associated with an enhanced chronic inflammatory response in the lung airways to noxious particles or gases. Exacerbations and co-morbidities contribute to the overall severity in individual patients."[2] Therefore, the importance of co-morbidities in COPD patients has been highlighted in the GOLD guidelines. Co-morbidities most commonly reported with COPD are cardiovascular diseases, cancer, cachexia, osteoporosis, depression and anemia.[3] Recent years, anaemia has been found to be an important co-morbidity in patients with COPD, though traditional emphasis is on the polycythemia with COPD. The real prevalence of anaemia in COPD is still not known, especially in India, but the studies from the West have suggested its prevalence to be 7.5% to 34%.[4] COPD and anaemia both are known to have fatigue and dyspnoea as their major symptoms. The co-existence of both the conditions is significant as it is associated with further worsened fatigue and dyspnoea with a negative impact on mental, physical and social functioning of COPD patients, leading to poor quality of life in them.[5,6] Anaemia also

increases the health care utilization, worsens the survival in COPD patients.[7] The link between the COPD and co-morbidities can be explained by systemic inflammation. Systemic inflammation in COPD may be the direct consequence of systemic "spill-over" of the ongoing pulmonary inflammation[8] or may be a part of chronic systemic inflammatory syndrome initiated by the COPD.[9] Because of these widespread extra-pulmonary effects of COPD, the disease outcome in terms of increased morbidity and mortality can be categorized by studying various parameters in these patients like Body Mass index, FEV1, Dyspnoea and exercise Capacity. These parameters are included in the multidimensional BODE index which is a better predictor of the morbidity and mortality in COPD than any individual parameter.[10] Persual of available literature regarding Health Related Quality of Life (HRQL) & BODE index in anaemic COPD patients revealed limited studies worldwide. In this study, we evaluated the frequency of anaemia in COPD patients and its impact on quality of life by the disease specific questionnaire – St George Respiratory Questionnare[11] and also explore and understand the BODE index in anaemic and non-anaemic COPD patients to ascertain the difference in the morbidity level between the two groups.

METHODOLOGY

Study Subjects : It was a an observational study conducted at Indira Gandhi Medical College, Shimla which is the tertiary care centre of Himachal Pradesh located in the north-western Himalayan region of India. It was conducted on all consecutive stable COPD patients attending the Outpatient Department of Pulmonary Medicine from June 2013 to June 2014. This northern state is having high prevalence of the COPD and this institute covers majority of the population of this state.

Study Design: The diagnosis of COPD was based on relevant clinical history and post-bronchodilator spirometry was performed according to American Thoracic Society/European Respiratory Society recommendations using a spirometer (Spirolab 11).[12] The diagnosis of COPD and its severity were determined according to GOLD criteria.[2] A written consent was obtained from all the eligible patients in the study who were clinically stable, ≥35years of age, suffering from mild to moderate COPD with SpO2≥90%.

Patients with history or clinical evidence of pulmonary disease or other chronic diseases like hypertension, diabetes mellitus, chronic kidney disease, thyroid disease, hepatic diseases were excluded. Patients were also excluded if they had any neuromuscular, musculoskeletal, peripheral vascular, cardiovascular disorders which limit the capacity to perform the 6-min walk test. All the patients underwent venous blood sampling and following parameters were measured: Hb levels, renal function tests, liver function tests, thyroid function tests. These stable COPD patients who were free from any morbidity (except anaemia) were then subjected to six minute walk test and St George Respiratory Questionnaire within one week of their first visit. Study protocol was approved by the institutional ethical committee.

Study Measurements: The demographic features of patient namely age, sex, height, weight and Body Mass Index (BMI) in kilogram per metre square were taken. The spirometric examination was done using Compact Vitallograph 2120 (Vitallograph, UK). The lung function indices included percent predicted of Slow Vital Capacity (SVC), Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second (FEV_1), and FEV_1/FVC and at least three measurements were recorded for each lung function variable and the best measurements were accepted as the final readings. Hemoglobin estimation was done with a **Fully Automated 3 part Differential Blood Cell Counter, Model MS-9 (Hd Consortium)** in the study population group. The anemia was defined as per WHO guidelines.[13] The World Health Organization defined anemia as hemoglobin level of less than 13 g/dL in men and 12 g/dL in women. The study population was divided into anaemics and non anaemics. The impact of anemia on health related quality of life was studied by St. George Respiratory Questionnaire. The patients of study population were seated at a quiet place to answer the questionnaire. For every option of the different questions of the questionnaire, scoring of 0 or 1 was done depending upon the absence and presence of the asked symptoms, consecutively. These scores were then entered into the St George Respiratory Questionnaire Calculator, to obtain the symptom score, activity score, impact score and the total score. Higher scores in any of these categories indicate a better Health Related Quality of Life. The BODE index was used to compare various clinical characteristics among anaemic and non anaemic COPD patients, which include four parameters namely-BMI, obstruction level (FEV1), dyspneoa level (mMRC dyspnoea score) and exercise tolerance (six minute walk test). Each component was graded and score out of 10 was obtained for individual patients by entering these variables into BODE index calculator. The

BODE score obtained, was then compared between the anaemic and non anaemic COPD patients, with higher scores indicating the greater risk. Exercise capacity was measured by the six minute walk test which was performed as per the ATS guidelines.[14] The pulse rate, blood Pressure and oxygen saturation was measured at the start and at the end of six minutes walk test. These parameters were measured using a portable pulse oximetery device (Lotus 300). The subjects were made to walk along 30 mtr long pathway at their comfortable speed and cover as much distance as possible in 6 minutes. They were allowed to stop if the distressing symptoms appear during the test but were asked to resume the walk if possible for them. The distance covered was measured in anaemic COPD and non-anaemic COPD patients.

Statstical Analysis: The continuous variables were described using means and Standard Deviation. Their means were compared using independent t test. The categorical variables distributed in the study population were described in percentages and analysed using Fischer exact test or chi square test, whichever applicable. Frequency of anaemia was determined in COPD patients. The variables found to have significant correlation in bivariate analysis were fitted in logistic regression model to assess independent predictive value. Two tailed significance $p<0.05$ was taken to be statistically significant. Statistical analysis was done using SPSS version 16, statistical software.

RESULTS

We analyzed the socio-demographic profile of the entire study population of 100 patients. The mean age of the patients was 62.6 years. The prevalence of anaemia in the study population was 32%. There was no significant difference in the mean age, gender distribution, smoking index and biomass exposure between anaemic and non-anaemic COPD patients. Comparison of COPD severity revealed non-significant difference between anaemic and non anaemic COPD patients (p=0.854). The lung function parameters had shown a decreasing but statistically non-significant trend in

the anaemic COPD patients as shown in Table 1. The analysis also revealed higher total SGRQ scores [37.3±18.07 vs. 34.8±19.1; p=0.53] and significantly higher symptom score in anaemic group [36.4±14.93) vs. 29.88±17.40; p=0.04] as in Table 2. The study of the BODE index parameters in both categories of patients revealed that the patients with anaemia had lesser BMI [(20.5±3.9) vs. (22.04±3); p=0.03], poor dyspnoea score [(1.7±.7) vs.(1.3±.9);p=0.05] and lesser six minute walk distance [(335.9±72.2) vs. (377.3±108.2);p=0.05] as compared to non-anaemics, as depicted in table III. The total BODE score was also significantly higher in anaemic COPD patients (p=0.01). These associations thus indicated decreased exercise capacity in them which is an evidence of poor quality of life.

Table 1: Represents the socio-demographic profile of the study subjects (N=100)

Variables	Subjects.
Age Years (mean±sd)	62.6± 8.72
Gender	
Males	69
Females	31
Education	
Illiterate	57
Literate	43
Occupation	
Government employee	14
Unemployed	86
Background	
Rural	87
Urban	13

Table 2: Clinical characteristics in anaemic and non anaemics on chi square test.

Variable	Anaemics (n=32)	Non-Anaemics (n=68)	p-Value
Age*	63 ±9.62	62.16 ±8.07	0.65
Gender (%)			
Males	26	43	0.07
Females	6	25	
Hb (gm %)	10.98 ±1.07	14.74 ±1.90	0.001
BMI(Kg/m²)*	20.48 ±3.97	22.04 ±3	0.03
Smoking Index	470.8±293.7	616.6±441.22	0.07

*Mean ±SD

Table 3: Represents the various components of BODE Index in Anaemics and non-anaemics

Variables	Anaemics*	Non Anaemics*	t Value	p-Value
Body Mass Index (Kg/m²)	20.48 ± 3.97	22.04 ± 3	2.19	0.03
FEV$_1$	1.06 ± 0.45	1.01 ± 0.44	0.46	0.65
mMRC Dyspnoea Level	1.66 ± 0.70	1.31 ± 0.85	2.01	0.05
6 minute walk distance in metres	335.88 ± 72.23	377.34 ± 108.19	-1.97	0.05

*Mean ± SD

Table 4: Various SGRQ scores in anaemics and non anaemic patients

Variable	Anaemics*	Non Anaemics*	t value	p-Value
Symptom	36.42 ± 14.93	29.88 ± 17.40	1.47	**0.04**
Activity	55.84 ± 10.84	55.53 ± 14.21	0.49	0.66
Impact	27.7 ± 26.4	23.11 ± 25.74	0.5	0.53
Total	38.4 ± 18.3	34.42 ± 18.92	0.63	0.32

*Mean ± SD

DISCUSSION

We evaluated hundred consecutive COPD patients (69 males and 31 females). Anaemia was detected in 32 patients. Therefore; the prevalence of anaemia in our study patients was 32%. John et al also compared the prevalence of anemia in various chronic diseases in hospitalized patients; COPD, heart failure, rheumatoid arthritis and cancer. The overall prevalence of anaemia in COPD patients was 23.1%, whereas prevalence in patients with chronic heart failure was 23.3%. Patients with renal insufficiency and cancer had the highest anemia frequencies of 71.8% and 45% respectively.[15] Chambellan et al.[16] studied patients with severe oxygen-dependant COPD, and anaemia (defined by haematocrit <39% in men and <36% in women) was present in 13% of men and 8% women. Cote and colleagues [17] in a retrospectively analysis reported anaemia in 116 (17%) patients. Another study by Halpern et al.[18] and Shorr et al.[19] identified anaemia in 21% and 33% of patients with COPD respectively. Highly variable frequency of anemia in COPD patients reflects different study design, outpatient versus hospitalized patients, local prevalence of anemia, and different definitions of anemia adopted. We analyzed the pulmonary function tests in these anaemic and non-anaemic COPD patients and found that anaemics had a higher level of obstruction as compared to non-anaemics, although, it was not statistically significant. But these findings did suggest that anaemics had more compromised pulmonary functions than non-anemic COPD patients. There are various mechanisms of anaemia in COPD patients; anemia of chronic disease, iron and vitamin deficiency, comorbidities, hypogonadism or treatment related.[20] However; most accepted hypothesis is the development of anemia of chronic disease (ACD), or anemia of Inflammation in COPD patients. ACD is an inflammation mediated phenomenon so is present in many chronic inflammatory conditions like COPD. Hepcidin is the main factor involved in ACD. Iron is liberated from the cell via ferroportin. Hepcidin causes destruction of ferroportin via lysosomal degradation.[21] Therefore; iron fails to get released and to reach the site of haematopoiesis. IL-6 is one of the signal for hepcidin

synthesis.[22] John et al[15] reported a significantly higher level of inflammatory parameters in anemic COPD patients compared to control subjects, IL-6 (p <0.0001) and CRP (p < 0.001). We analysed the HRQL in patients with COPD by using the St George Respiratory Questionnaire. In the entire study population (n=100), respondents with anaemia had a higher symptom score, higher activity score, higher impact score (table 4) and higher total score. (graph 2). Larger are the SGRQ scores, greater is the impact of the disease on the COPD patients and worse is their health related quality of life. These higher scores of various components of SGRQ predict a greater impairment of physical activity and higher level of psychological impact in anaemic COPD patients. In our study, we achieved significantly higher symptom scores in anaemic COPD patients (36.42±14.93 vs.29.88±17.40) p=0.04), thereby indicating that these patients are much more symptomatic than non-anaemic COPD patients. This finding is also supported by a study by Krishnan et al.[23] They retrospectively analyzed the relationship between anemia in COPD and HRQL amongst patients enrolled from the general population in New York city. This study used generic instrument, SF-36 rather than a disease specific QOL instrument. Among patients with COPD, the physical functioning (PF) scores and the physical component summary scores were significantly lower in individuals with anaemia compared to those without anaemia. So, this study concluded that in patients with moderate to severe COPD, anaemia may be associated with worse HRQL. The limitation of this study is that some of the disease processes that may confound the results are not adjusted e.g. congestive heart failure and neuromuscular disorders. We have ruled out co-morbidities in our study. Anaemia causes fatigue and dyspnoea and fatigue is also an important symptom in COPD, present in 43 to 58% of patients with COPD.[24] Both of these symptoms can be attributed to poor quality of life (QOL) of COPD patients. Cote et al[6] reported anemia as an independent risk factor for reduced functional capacity in COPD patients. Celli et al proposed that any single parameter of pulmonary functions is not a better predictor of morbidity and survival than the composite scoring systems like BODE index

which include indicators from various dimensions of the disease.[10] This grading system is multidimensional, so it can assess the respiratory and systemic expressions of COPD and can better predict the outcome in COPD patients, with respect to morbidity. We used this scoring system in anaemic and non-anaemic COPD patients and found lesser mean BMI in anaemic COPD patients than that in non-anaemic COPD patients (20.48±3.97 vs. 22.04±3Kg/m^{2} p=0.03). Botou et al[7] also reported a lower mean BMI in anaemic COPD patients than non-anaemic COPD patients though, the difference was insignificant (p= 0.296). Dyspnoea, another major component of BODE index, is the foremost symptom of COPD. This symptom can get aggravated due to the simultaneous presence of anaemia in COPD, because the anaemia decreases the oxygen carrying capacity of blood, thereby increasing the ventilatory drive, thus resulting in dyspnoeic symptoms. Schönhofer et al[25] evaluated the impact of blood transfusion on minute ventilation (V'E) and work of breathing (WOB) in 20 anemic adults (hemoglobin of <11 g/dl) including ten severe COPD patients and ten patients with no underlying lung disease. Blood transfusion decreased the mean V'E from 9.9 ± 1.0 to 8.2 ± 1.2 L/min (p < .0001), and, WOB from 1.03 ± 0.24 to 0.85 ± 0.21 WOB/L (p < .0001) in patients with COPD. In anemic patients without lung disease, minute ventilation and WOB did not change by a similar degree. Therefore, in COPD patients with anemia, blood transfusion leads to a significant reduction of both the V'E and the WOB. The low arterial oxygen concentration leads to early anaerobic metabolism, resulting in lactate production, which could serve as a cause for high ventilatory drive and increased dyspnoea due to the stimulation of peripheral chemoreceptors. The mMRC dyspnoea score in our study was found to be 1.66±.70 in anaemic COPD patients and 1.31±.85 in non-anaemic COPD patients with a p value of 0.05. In a study by Cote et al[17], anaemic COPD patients had significantly higher mMRC dyspnoea score (2.8±0.9) than non anaemic COPD patients (2.6±0.8) with p value 0.04. Anaemia was an independent predictor of increased dyspnoea in this study.The three factors of low BMI, higher airflow obstruction and increased dyspnoea results in poor exercise capacity in anaemic COPD patients, which is supported by the results of six minute walk test in our study. The results suggested lesser mean walking distance (335.88 m ±72.23) in anaemics than non-anaemics (377.34 m ±108.19) with a significance of p= 0.05. This finding was supported by the study by Cote et al[(17)]. It was the first study to demonstrate increased functional impairnment and decreased exercise capacity in COPD due to anaemia. This study found that the mean 6MWD (six minute walking distance) was significantly shorter (265±122 m vs 325±124 m; p<0.0001). These four parameters culminate into BODE score which among the anaemics was 2.91, compared to 1.99 in non anaemics with a significant (p=0.01) statistical difference.

CONCLUSION

Our study validates that anaemia is common, chronic, co-morbidity in COPD patients, with the prevalence of 32%. Our study also concludes a significant association of larger BODE score and anaemia in COPD thereby indicates poor quality of life and greater morbidity in them. Hence, it is concluded that COPD patients should be subjected to BODE scoring as a part of regular management. SGRQ has also proven to be a reliable method of assessing the health related quality of life of anaemic COPD patients.

The high prevalence and the large impact of anaemia on COPD, points towards the need of regular screening and adequate treatment of COPD patients for anaemia to improve their quality of life. Hence, treatment and screening for anaemia should be included in the standard treatment guidelines for COPD.

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