Tanaffos (2009) 8(2), 11-16

Anemia in COPD Patients and Its Relation to Serum Levels of Erythropoietin

Davood Attaran [1], Mohammad Khajedalouee [2], Fereydoon Ahmadi [3], Fariba Rezaeitalab [1], Mohammad Towhidi [1], Amir Asnaashari [1], Mahasti Babaeian [1], Saman Rezaei [4], Shahrzad M Lari [1]

[1] Department of Pulmonary Diseases, Lung Disease and Tuberculosis Research Center, [2] Department of Public Health, [3] Department of Hematology, [4] Otorhinolaryngology Ward, Mashhad University of Medical Sciences, MASHHAD- IRAN.

ABSTRACT

Background: *Although chronic obstructive pulmonary disease (COPD) is traditionally associated with polycythemia, its systemic inflammatory components can interfere with erythropoietin and result in anemia of chronic disease. We assessed the frequency of anemia and its relation to serum erythropoietin (EPO) levels and severity of the disease in a group of COPD patients.*

Materials and Methods: *Eighty patients with the mean age of 66.48 ± 11.55 years and mean forced expiratory volume in first second (FEV1) of 45.14 ± 16.88 % predicted were enrolled in this study. Severity of the disease was defined according to the global initiative for chronic obstructive lung disease (GOLD) guidelines. Hemoglobin and erythropoietin levels were assessed in all patients.*

Results: *Anemia of chronic disease was present in 13 of 80 patients (16%). The mean serum levels of EPO were 59 ± 203 (SD) µ/l and 70.3 ± 255 (SD) µ/l in anemic and nonanemic COPD patients, respectively. There was no significant difference between the two groups (p=0.13). A significant correlation was seen between hemoglobin and serum EPO in all COPD and nonanemic patients (r = - 0.86, p<0.001 and r = - 0.28, p = 0.02). No significant correlation was seen between hemoglobin and serum erythropoietin levels in the anemic group (r = 0.07, p = 0.82).*

Conclusion: *This study showed that anemia occurred relatively frequently in COPD patients. In addition to erythropoietin resistance, other factors are probably involved in the pathogenesis of anemia in these patients.* ***(Tanaffos 2009; 8(2): 11-16)***

Key words: *Anemia, COPD, Erythropoietin, Hemoglobin*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by the progressive development of airflow limitation that is not fully reversible. It is currently accepted that an excessive inflammatory response of the lungs to a variety of noxious inhaled gases or particles mostly cigarette smoking is a key in the pathogenesis of COPD (1). Recent studies have provided evidence that COPD is often associated with significant extrapulmonary abnormalities, called "systemic effects of COPD" (2,3). These effects are mostly due to increased levels

Correspondence to: Lari SM
Address: # 2/99, Asrare-Gharbi, Koye-Doctora, Mashhad, Iran
Email address: larish851@mums.ac.ir
Received: 12 July 2008
Accepted: 27 March 2009

of proinflammatory cytokines such as interleukin 1 (IL-1), IL-6 and tumor necrosis factor α (TNF-α) (4-6).

Anemia is seen in many chronic diseases such as heart failure, rheumatoid arthritis, cancer and chronic renal disease (7,8). It occurs relatively frequently in COPD patients and is related to the presence of inflammation; it is an understudied issue in COPD but may be of great importance in this disease (9). John et al. found that among 101 severe COPD patients, 13 were anemic (9).

COPD-related inflammation could also impair erythropoiesis, as do other chronic inflammatory processes (10-13). Hemoglobin levels in COPD patients would reflect the balance between the stimulation of erythropoiesis by hypoxia and its depression by inflammation (10). Erythropoietin (EPO) is an endogenous glycoprotein hormone that serves as the primary stimulus for erythropoiesis. Recent evidence has demonstrated that anemic COPD patients show high erythropoietin levels which may indicate the presence of erythropoietin resistance and they exhibited significant elevated levels of EPO compared to non anemic patients (9).

Inadequate hemoglobin levels could aggravate tissue hypoxia, worsen dyspnea, and limit exercise tolerance (10, 14). In the study of COPD population by celli et al, patients who died had a significantly lower hematocrit than those who survived (15).

The present study was conducted to assess the frequency of anemia in a group of COPD patients and its correlation with severity of disease and serum EPO levels.

MATERIALS AND METHODS

This study was conducted on COPD patients referred to the pulmonary clinic of Ghaem Hospital, Mashhad, Iran, between April 2006 and Feb. 2007. COPD was diagnosed according to the guidelines of American Thoracic Society (16), i.e. FEV_1< 80% of predicted and FEV1/FVC < 0.7 with FEV_1 change of less than 200 ml and 12% in the postbronchodilator test.

The exclusion criteria were as follows: 1- asthma, defined as an increase in FEV_1 more than 12% and 200 ml above baseline after administration of a short acting bronchodilator; 2- patients with cancer, severe liver or kidney diseases, left heart failure, or other chronic diseases; 3- history of gastrointestinal bleeding or blood loss of any other cause; 4- vitamin B12 or folic acid deficiency (microcytic and macrocytic anemia); 5- low ferritin serum levels (less than 100 ng/ml); 6- positive drug history for ferrous sulfate, folic acid, and vitamin B_{12}.

The severity of COPD was assessed using FEV_1 measures based on the global initiative for chronic obstructive lung disease (GOLD) guideline (1). All patients were clinically stable and receiving routine standard therapy for COPD.

The study was approved by the ethics committee of Mashhad University of Medical Sciences and all patients gave an informed consent. FEV_1 and FVC were measured with standard spirometric technique (chest, Japan) before and 10-15 min after inhalation of two puffs of salbutamol. All values of spirometric parameters were expressed as a percentage of their predicated values. Anemia was diagnosed by hemoglobin levels less than 13.5 g/dl in male patients and less than 12 g/dl in female patients (17).

Following parameters were assessed in each patient: arterial blood gas, complete blood count, red blood cell indices, serum iron, TIBC and ferritin levels, serum EPO levels, and body mass index (BMI). Arterial blood gas and pH were measured on a blood sample from radial artery. Cell blood counts and red blood cell indices were determined by an automated H analyzer. Serum EPO levels were determined by an enzyme linked immunosorbent assay (IBL, Germany) on venous blood sample collected in the morning. The BMI was calculated as the ratio of weight (kg) to height (m) in squared.

Statistical analysis:

The data were analyzed by using SPSS software version 11.5. For analyzing the effect of BMI on severity of COPD, Kruskal-Wallis test was used. Comparison of quantitative variables between

anemic and nonanemic groups was done by independent t-test and Mann-Whitney test. For analysis of the association between hemoglobin and EPO, Spearman correlation coefficient was applied. For analysis of qualitative variables, Chi-square test was used. P-values less than 0.05 were considered significant.

RESULTS

Among 115 patients enrolled in this study, 80 were eligible for analysis (53 males and 27 females, mean age of 66.48±11.55 years and FEV_1 1.04±0.39 lit, and 45.14±16.88 % predicted.). There was a history of smoking in 76 patients (95%). Grading of disease severity revealed that 6 patients (7.5%) had mild, 18(22.5%) had moderate, another 18 had (22.5%) severe, and 38 patients (47.5%) had very severe COPD.

Normochromic normocytic anemia was present in 13 patients (16.3%). Demographic data and clinical characteristics of patients with or without anemia are shown in Table 1. There was no significant difference in BMI between anemic and nonanemic patients (p=0.91). There was no significant difference in age, sex, severity of COPD, and blood gas parameters between anemic and nonanemic COPD patients (Table 1). The mean hemoglobin levels for anemic and nonanemic patients were 12.23 ± 0.97 and 15.66 ± 1.50 g/dl, respectively (p= 0.0001). There was no significant difference in mean serum EPO levels between anemic and nonanemic patients (59±203 and 70.3±255 μ/l, respectively; p=0.13). Correlation analysis showed a significant correlation between hemoglobin and serum EPO levels in all subjects with COPD and in nonanemic patients as well (r=-0.86, p=<0.001 and r=-0.28, p=0.02, respectively) (Figures 1 and 2). There was no significant correlation between hemoglobin and serum EPO in anemic patients (r = 0.07, p = 0.82) (Fig. 3).

The majority of anemic patients (70%) had severe COPD. Classification of COPD severity in anemic and nonanemic patients is shown in Table 2.

Table 1. Demographic data and clinical characteristics of the patients

Variable	Anemic group	Nonanemic group	P value	CI
Subjects	13	67		
Age (y)	67.84 ± 9.76	66.22 ± 11.91	0.64	(-5.38 to 8.63)
FEV_1(% predicted)	48.3 ± 14.15	44.52 ± 17.11	0.37	(-6.31 to 13.87)
FVC(% predicted)	65 ± 13.57	57.36 ± 16.77	0.57	(-0.37 to 0.49)
FEV-1 %	54.91 ± 8.12	52.56 ± 8.39	0.86	(-0.2 to 0.27)
BMI ($kg.m^2$)	26.45 ± 5.58	26.13 ± 5.30	0.91	(-2.9 to 3.55)
PaO2 (mmHg)	61.75 ± 12.65	63.011 ± 14.45	0.90	(-8.8 to 8.25)
P_aCO2 (mmHg)	52.11 ± 11.02	57.59 ± 12.57	0.1	(-12.29 to 1.96)
Hgb (g/dl)	12.2 ± 0.97	15.66 ± 1.50	<0.001	(2.59 to 4.33)
Erythropoietin (U/L)	59 ± 203 (Median:1.6)	70.3 ± 255 (Median:0.89)	0.13	(-160.32 to 138.74)
TIBC (μg/dl)	353.54 ± 34.72	312.46 ± 82.13	0.08	(-5.24 to 87.40)
Ferritin (ng/ml)	326.63 ± 211.82	176.18 ± 62.6	<0.001	(106.73 to 194.17)

Data were presented as mean ± SD

FEV1: forced expiratory volume in first second, FVC: forced vital capacity, BMI: body mass index,

PaO_2: arterial oxygen pressure, PaCO2: arterial CO2 pressure, Hgb: hemoglobin, TIBC: Total Iron Binding Capacity

CI: Confidence Interval

Table 2. Classification of the severity of disease in anemic and nonanemic COPD patients

Variable	Total (%)	Anemic group (%)	Nonanemic group(%)
Mild COPD	5 (6.25%)	0 (0%)	5 (7.4%)
Moderate COPD	18 (22.5%)	3 (23.1%)	15 (22.4%)
Severe COPD	39 (48.75%)	9 (69.2%)	30 (44.8%)
Very severe COPD	18 (22.5%)	1 (7.7%)	17 (25.4%)
All subjects	80 (100%)	13 (100%)	67 (100%)

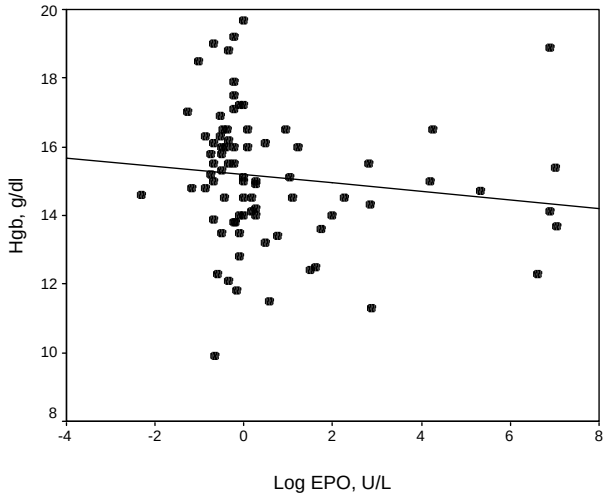

Figure 1. The correlation between hemoglobin and serum erythropoietin levels in all COPD patients (r = -0.86, p < 0.001)

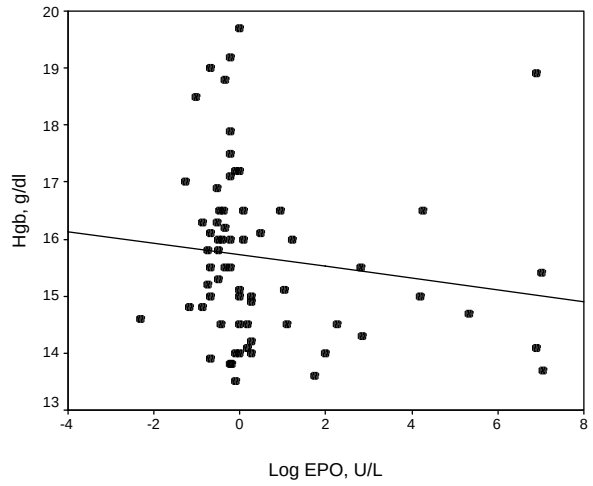

Figure 2. The correlation between hemoglobin and serum erythropoietin levels in nonanemic patients (r = -0.28, p = 0.02)

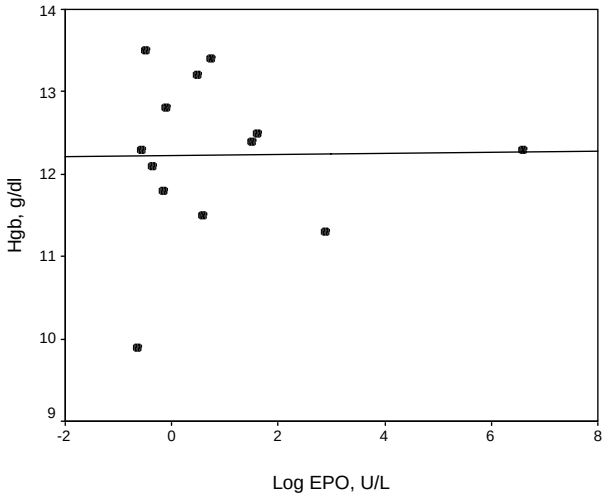

Figure 3. The correlation between hemoglobin and serum erythropoietin levels in the anemic group (r = 0.07, p = 0.82)

DISCUSSION

Anemia is an underestimated issue in COPD, but with a great importance in this disease. In the present study, anemia was prevalent (16%) among patients with COPD. The prevalence of anemia identified in the present study is similar to that reported in recent studies on COPD.

Gastrointestinal bleeding, chronic renal failure, and deficiency in vitamin B_{12}, folate or iron can coexist with COPD and should not be overlooked in anemia of COPD patients. Therefore, we excluded patients with anemia related to bleeding, B_{12} and folate deficiency, or other chronic disorders. COPD itself might cause anemia due to chronic disease. Shortened survival of red blood cells is thought to be the result of raised levels of IL_1, IL_6, and TNFα (18,19). These findings are common in COPD and exaggerated during its exacerbations (12). Inflammatory cytokines also decrease the EPO response to hypoxemia, impede iron utilization, and impair bone marrow EPO response. This is caused by a relative EPO resistance due to an impaired ability of red blood cell progenitors to respond to EPO (20-22). This study showed that EPO serum level was

higher than normal in these patients. Although there were significant correlations between hemoglobin and EPO levels in all of our understudy patients as well as in the nonanemic group, no significant correlation was found in anemic patients. Therefore, apart from EPO resistance, other factors may also contribute to the lower hemoglobin levels in COPD patients. Defective EPO production and impaired iron utilization due to inflammatory markers are additional pathogenic factors (9). It must be emphasized that factors other than inflammation can be responsible for anemia in COPD patients. Malnutrition, tobacco smoking (because of its associated oxidative stress), and finally oxygen therapy can theoretically blunt hypoxia-driven erythropoiesis in COPD patients (23).

In Chambellan et al. study, there was a correlation between anemia and other factors like age, COPD severity, BMI, and blood gas parameters (10). The results of our study showed no correlation between anemia and these factors.

The present study is limited by: 1) A relatively small number of understudy patients; another study with a larger sample size is required for better determination of the correlation between anemia and disease severity and for testing the hypothesis that correction of anemia may improve the outcome in COPD patients. 2) We ruled out combined anemia (microcytic and macrocytic) only by measuring serum iron, TIBC, and ferritin. It would be better if serum vitamin B_{12} and folate levels were measured too.

In brief, currently available arguments suggest that: 1) hemoglobin status in COPD patients could be determined by the balance between the stimulating effects of hypoxia on EPO production and inflammation-induced EPO resistance; 2) as with heart failure, anemia could have a negative prognostic impact on COPD, associated with reduced survival and increased morbidity; 3) anemia could aggravate dyspnea and exercise capacity (24).

Our study results showed that anemia was prevalent in COPD patients and clinicians should be aware of that. A deficient increase in EPO levels, decreased marrow responsiveness and impaired erythropoiesis due to inflammatory markers, and probably some other factors are involved in the pathophysiology of anemia.

Acknowledgement

This study was supported by the research chancellor of Mashhad University of Medical Sciences. We would like to thank Dr. Ghaffarzadegan for laboratory analysis.

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