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The relation among to mortality rate, hospitalization period and inflammatory mediators in patients with chronic obstructive pulmonary disease attack on admission to emergency department

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is characterized by a progressive and not completely reversible obstruction of the airways associated with an abnormal inflammatory response of the lungs to particles and noxious gases related to a systemic effect. Inflammatory processes are suggested to be involved in pathogenesis of COPD. The aim of the study was to investigate the relation among to the mortality rate, hospitalization period and inflammatory mediators of the patients with COPD attack on admission into the emergency department. A total of 87 subjects with COPD attack were contributed in this study. TNF-α, IL-6 and catalase were determined in addition to leucocyte count (WBC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). There was no significant difference between the deceased and discharged patients in terms of WBC, ESR, CRP, IL-6, and TNF-α. However, mean catalase levels of discharged patients were significantly higher than the deceased patients ($p<0.05$). Significant correlations were observed between WBC and hospitalization period, and CRP and follow up period in the intensive care unit. We can suggest that catalase activities on admission into the emergency service were decreased in deceased patients who were in follow up in intensive care unit with COPD attack. High CRP and WBC levels were also related with the hospitalization period of patients with COPD attack.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by a progressive and not completely reversible obstruction of the airways associated with an abnormal inflammatory response of the lungs to particles and noxious gases related to a systemic effect (Folchini et al., 2011). Patients with COPD frequently present exacerbations, which are a top-ranking social health-care problem because of their negative influence on the quality of life lung function and prognosis of these patients in addition to social and financial costs (Kersul et al., 2011).

The pathogenesis of COPD exacerbation episodes is not fully understood. There are different studies demonstrating that these episodes are characterized by an increase in various inflammatory markers, including the number of neutrophils and macrophages in the airway and the concentration of cytokines, particularly TNF-α, IL-6 and IL-8 (Bhowmik et al., 2000; Fujimoto et al., 2005; Joppa et al., 2006). Oxidative stress plays an important role in lung damage and inflammatory response in COPD. Oxidative stress may affect extra-cellular matrix remodeling, mitochondrial respiration, cell proliferation and lung defense mechanisms. Repair

mechanisms and the immune modulation system are directly affected by oxidative stress, which is one of the main events in inflammatory response (MacNee, 2001). Catalase is an antioxidant enzyme and decomposes hydrogen peroxide into water and oxygen. Recent findings suggest that the significance of catalase in pulmonary defence, especially at the alveolar level is important (Rahman et al., 2006).

The aim of the study was to investigate the relation between the mortality rate, the hospitalization period of the patients with COPD attack in the emergency department or intensive care unit and blood levels of TNF-α, IL-6 and catalase on admission.

2. Materials and methods

Patients

A total of 87 subjects (32 female and 55 male) who were previously diagnosed with COPD and admitted to emergency department with COPD attack between May 2013 and May 2014 were contributed in this study. This study was performed after ethical approval by the ethics committee of our faculty. Each case included in the study was informed about the study and written consents were obtained. When there were two or more of the symptoms presented in Table 1, the patient was diagnosed as COPD attack. All of the cases were smokers. Full physical examination; conventional anteroposterior X-ray and computed tomography of thorax were performed for all the subjects. The medicines used, oxygen therapy received and the number of attacks with hospitalization were also recorded. Inclusion and exclusion criteria are listed in Table 1. When any one of the diseases listed in Table 1 was existed, this subject was exluded from the study. All of the participants were monitored until their dischargings or mortalities. Duration of hospitalization in emergency service or intensive care unit was recorded.

Evaluation

After determination of vital signs arterial puncture was performed while resting and before oxygen supplementation to evaluate arterial blood gases. Venous blood samples of the patients were obtained from the participants at time of admission to emergency department for routine biochemical tests (hemogram, glucose, urea, creatinine, sodium, potassium, erythrocyte sedimentation rate (ESR) and CRP) and remaining serum portions were aliqoated and stored until analysis of the cytokines and catalase activities.

Serum IL-6 and TNF-α levels were determined by ELISA technique with Human IL-6 and Human TNF-α kits (BenderMed Systems, USA). The results were expressed as pg/ml. Inter and intra assay CV values determined by the manufacturer were 5.2% and 3.4% for IL-6 while 7.4% and 6% for TNF-α assays. Catalase activities were quantified with colorimetric method by using Catalase Assay kit (Cayman Chemical Company, USA). Catalase activities were expressed as nmol/min/ml. Intra and inter assay CV values for this assay were 3.8% and 9.9%, respectively.

Statistical analysis

Statistical analysis was performed with SPSS (version 18.0). Since all the demographic data and laboratory test results were compared between the discharged and died patients, Mann Whitney test was used for comparison of the medians. Pearson correlation analysis was used for bivariate correlation of the demographic data and the laboratory tests. $p<0.05$ was assumed as statistically significant.

3. Results

Among 87 subjects, 23 (mean age: 68.8±1.4) were hospitalized in intensive care unit and 64 (mean age: 68.8±9.5) in the emergency service. Pneumonia was diagnosed in five cases (3 in emergency service and two in intensive care unit). Seven cases in intensive care unit died during the follow-up, however all the patients monitored in the emergency service were discharged after treatment.

There was no significant difference in terms of pH, PaO_2, $PaCO_2$ and SaO_2 values between the subjects died in intensive care unit and discharged from the emergency service ($p>0.05$) (Table 2).

Mean hemoglobin and CRP levels, leucocyte count and ESR on admission to the emergency service were similar in died and discharged cases. As well as there was no significant difference for IL-6 and TNF-α levels between these two groups ($p>0.05$) (Table 2). Mean catalase activities of the discharged cases on admission to the emergency service were significantly higher than the activities of the cases who died ($p<0.05$) (Table 2).

Table 1. Inclusion and exclusion criteria for establishing the study population

	Inclusion	Exclusion
Symptoms/Signs	Dyspnea	
	Increased and/or purulent mucus	
	Fever	
	Wheezing	
	Edema	
	Decreased daily performance	
Disease		**Heart failure**
		Diabetes mellitus
		Acute/chronic renal failure
		Chronic liver disease
		Cancer
		Cerebrovascular disease
		Rheumatoid arthritis

Table 2. Laboratory test results of the patients with COPD attack on admission to emergency service

Parameters	Discharged patients (n=80)	Deceased patients (n=7)	p b
pH	7.38±0.10a	7.34±0.10	NS
$PaCO_2$ (mmHg)	49.05±20.5	52.28±16.22	NS
PaO_2 (mmHg)	63.26±24.25	55.56±16.07	NS
HCO_3 (mEq/l)	27.74±6.79	22.33±2.51	NS
SaO_2 (%)	87.31±12.10	83.76±8.45	NS
IL-6 (pg/ml)	11.55±8.18	15.02±20.08	NS
TNF-α (pg/ml)	27.47±4.34	24.47±3.53	NS
Catalase (nmol/min/ml)	83.08±26.84	62.70±8.69	0,045
ESR (mm/h)	29.09±18.71	32.00±34.77	NS
Hemoglobin (g/dl)	12.74±2,09	13.16±1.74	NS
WBC (K/µl)	12.25±11.51	14.14±3.17	NS
CRP (mg/l)	46.40±38.47	48.91±45.89	NS
Duration of follow up in ICU (day)		11.0±11.40	NS
Duration of follow up in emergency service (day)	6.22±7.86		

[a] Mean±SD values for each parameter were given in the table.
[b] Groups were compared with Mann Whitney test and p values were assigned as significant when p<0,05.
COPD: Chronic obstructive pulmonary disease; **ESR:** Erythrocyte sedimentation rate; **WBC:** White blood cell/leucocyte count; **CRP:** C-reactive protein; **ICU:** intensive care unit

There was a weak negative correlation between oxygen saturation (SAT) values and TNF-α levels on admission (r=-0.294, p=0.016), and a strong positive correlation between leukocyte count and the hospitalization period (r=0.733, p=0.000). A significant positive correlation was also observed between CRP levels and hospitalization period at intensive care unit (r=0.487, p=0.025) (Table 3).

4. Discussion

In this study we have evaluataed the relation between the mortality rate, hospitalization period of the patients with COPD attack in the emergency department or intensive care unit and blood levels of TNF-α, IL-6 and catalase on admission. Catalase activities significantly decreased in patients who died during follow up in intensive care unit. However there was no significant difference for the other parameters tested between the discharged and deceased patients. Due to the correlation analysis we can suggest that the duration of hospitalization period was related with leukocyte count and CRP levels.

Under normal circumstances, antioxidant system and oxidants function in tissues properly. The most important enzymes that function in the antioxidant system are glutathione peroxidase (GSH), catalase and superoxide dismutase (SOD). If the cases with COPD expose to an agent that can trigger the disease, the balance will change in favor of oxidants. These enzymes fail to destroy lipid peroxidation items (Rahman et al., 2006; Mak 2008; Lakhdar et al., 2011).

Oxidative stress indicators and antioxidant enzyme levels were determined in a study planned to determine the severity of the attack of COPD. Antioxidant enzyme levels (catalase, GSH, SOD) of the cases with serious and very serious COPD attack were lower than those of the cases with mild attack however oxidative stress indicators were increased (Folchini et al., 2011). Our results dealing with catalase activities are in agreement with the findings of this previous report.

According to the findings of our study, CRP levels on admission can be suggested as a predictor of the duration of hospitalization period in the intensive care unit. Our results are in concordance with most of the previous reports. In the previous studies, CRP levels of the cases with COPD attack were mainly used to determine the requirement to antibiotic treatment and the respond to treatment. There are plenty of studies reporting that CRP level is a proper inflammatory indicator and a proper follow-up parameter during the treatment of inflammation (Antonescu-Turcu and Tomic, 2009; Dahl and Nordestgaard, 2009). Daniels et al. (2010) have reported that COPD inflammation correlates mildly with CRP and procalcitonin levels and there is a relation between the CRP levels and the existance of bacterium in the airways. CRP levels of the cases with COPD attack, who are being hospitalized, can be a guide for the requirement of antibiotic treatment and follow-up (Bafadhel et al., 2011).

It has been stated in a study carried out on patients with COPD considering their CRP levels that CRP can be a determiner for outcome assessment (Man et al., 2008). Dahl (2009) has established that high CRP level in patients with COPD is a free predictor for hospitalization and death. On the other hand, de Torres et al. (2008) have found that CRP level is not related with survival in case of mild and severe COPD attack.

High CRP level in patients with COPD inflammation is associated with severe clinical response, particularly with shortness of breath felt more severely during mabilization. Besides, high CRP level is closely associated with recurrent attacks and increased hospitalization rate. High CRP level is the indicator of not only the high hospitalization and mortality rate but worse pulmonary functions and bronchial hyperreactivity as well (Stevans et al., 1992; Garrod et al., 2007; Dahl and Nordestgaard, 2009).

Moreover, the fact that leucocyte count which is a primary follow-up indicator of inflammation correlated with the duration of hospitalization in our study suggests that the leucocyte count on admission can be an important prognostic indicator in the cases with COPD.

According to the findings of our study, IL-6 and TNF-α level on the admission with COPD attack are not determinants for hospitalization period and mortality. This result suggests that serum IL-6 and TNF-α might not be increased in the early phase of the attack. Therefore, IL-6 and TNF-α are not convenient determinants for prognostic evaluation of the patients with COPD attack.

Table 3. Correlation analysis between hospitalization period in emergency service or intensive care unit and laboratory test results

		Catalase	TNF-α	IL-6	WBC	ESR	CRP
Duration of follow up in ES	r	0.003	-0.161	0.004	0.733	0.002	-0.005
	p	0.987	0.296	0.980	0.000	0.992	0.977
Duration of follow up in ICU	r	-0.038	-0.261	-0.094	0.272	0.166	0.487
	p	0.864	0.230	0.669	0.209	0.554	0.025

WBC: White blood cell/leucocyte count; **ESR:** Erythrocyte sedimentation rate; **CRP:** C-reactive protein; **ES:** Emergency service; **ICU:** intensive care unit

TNF-α is a proinflammatory cytokine that has a regulatory effect on the pulmonary circulation. IL-6 is a potent stimulant cytokine for the secretion of CRP from the liver. Besides, it is known fact that it is an independant risk factor for cardiovascular events (Stevans et al., 1992; Ridker et al., 2000).

Joppa et al. (2006) evaluated the levels of CRP, TNF-α and IL-6 in order to evaluate systemic inflammation level in the cases with and without pulmonary hypertension. As a result, they found that CRP and TNF-α level in the COPD cases with pulmonary hypertension were higher. They have reported that a lower systemic inflammation level will decrease the risk for the development of pulmonary hypertension.

TNF-α and IL-6 levels were considered as the early parameters on admission of the cases to the emergency service. However, Ko et al. (2009) have reported that TNF-α levels of the cases with COPD inflammation reached its highest level on the 14th day after being discharged and this was statistically significant. If the measurements of TNF-α and IL-6 levels had been repeated at regular intervals during their stay in the intensive care unit and follow-up period, different results might have been obtained.

CRP, IL-6 and leucocyte count are considered as markers of inflammation in COPD by ECLIPSE study also. To further evaluate the pathogenesis and prognosis of COPD attack some genomic evaluations, and analysis of sputum and exhaled breath were also added. However mortality rates are still high and hospitalization periods are long in these patients (MacNee et al., 2011; Qiu et al., 2011; Celli et al., 2012; Miller et al., 2013; Siedlinski et al., 2013).

Our study has some limitations. Firstly our sample size is small for such a study. However in one year period we have included all of the available cases who did not present any of the exclusion criteria in our study. Secondly we could measure the tested parameters (TNF-α, IL-6 and catalase) only once on admission to the emergency service. If we could repeat the measurements we might have found significant increases in cytokine levels. However our budget for this study was limited, so we could not perform any other measurements.

We can suggest that catalase activities on admission to the emergency service were decreased in deceased patients who were in follow up in intensive care unit with COPD attack. However TNF-α, IL-6 levels on admission were not significantly increased in patients with COPD attack. According to our findings high CRP levels and leucocyte count were related with the duration of hospitalization in these patients. More conclusive findings can be obtained from the studies with larger sample sizes and with serial measurements of these parameters at certain intervals.

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