Procalcitonin: Is it a predictor of noninvasive positive pressure ventilation necessity in acute chronic obstructive pulmonary disease exacerbation?

Ahmet Cemal Pazarli, Handan Inonu Koseoglu, Sibel Doruk, Semsettin Sahin1, Ilker Etikan2, Serhat Celikel, Bahadir Berktas
Departments of Pulmonary Diseases, Biochemistry, Biostatistics, Gaziosmanpasa University, Tokat, Atatürk Chest Disease and Surgery Education and Research Center, Ankara, Turkey

Background: Acute exacerbations of chronic obstructive pulmonary disease (AeCOPD) are important causes of morbidity and mortality. In this study, we analyzed procalcitonin (PCT) levels in AeCOPD and stable period of COPD in order to evaluate usage of PCT in the prediction of the severity of AeCOPD, and its value on the planning of noninvasive positive pressure ventilation (NPPV).

Materials and Methods: In this cross sectional study (2009-2010) 118 COPD patients were enrolled, 68 of them (58%) were in acute exacerbations (case group). The others had stable COPD and they were defined as control group.

Results: In case group the mean levels of PCT (0.19 ± 0.02) C-Reactive Protein (44.7 ± 5.92), erythrocyte sedimentation rate (28.4 ± 2.65), white blood cell (9.4 ± 0.43) and %neutrophils (69.9 ± 1.22) were significantly higher than controls (P = 0.0001). There was no difference between PCT levels based on stages of COPD. There were significant differences in mean PCT levels according to type and severity of AeCOPD. Mean PCT level in hospitalized patients receiving NPPV was 0.36 ng/ml, while it was 0.15 ng/ml for those treated without NPPV (P = 0.0001). PCT cut-off value for NPPV indication was determined to be 0.10 ng/ml.

Conclusions: PCT levels were found to be higher in AeCOPD patients than in stable COPD patients, as expected. Also mean PCT levels increased especially in cases with severe AeCOPD and those receiving NPPV among them. In the present study, we determined a cut off value of PCT as 0.10 ng/ml as a predictor of necessity of NPPV in AeCOPD.

Key words: Acute exacerbation, chronic obstructive pulmonary disease, procalcitonin, noninvasive positive pressure treatment

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterised by chronic airflow limitation associated with the inflammatory process of the lung.[1,2]

Acute exacerbations of COPD (AeCOPD) are characterized by dyspnea, increase in the production and purulence of sputum.[3] These AeCOPDs impair the health status of the patients, accelerate progression of the disease, and increase in healthcare costs also it may cause death if respiratory failure develops. Sometimes, AeCOPD is mild and can be treated at home. However some of them requires hospitalization even in intensive care unit.[3] The severity of the exacerbation should be determined when deciding on treatment.

A 50-60% of AeCOPD are because of infection. Approximately half of the exacerbations due to bacterial infection, 30% of them due to viral infection and 5-10% of them due to atypical bacterial infection.[4] Procalcitonin (PCT) as a good marker is frequently used to reveal the presence of a bacterial infection. It is a polypeptide composed of 116 amino acids with a molecular weight of 13 kDa.[5,6] Its serum level markedly increases especially in bacterial infections, it does not change in viral infections or autoimmune inflammations.[7,8] In comparison with C-reactive protein (CRP), as demonstrated in the literature, diagnostic accuracy of PCT in proving bacterial infection is relatively higher, while it is more sensitive, and specific in differentiation between bacterial infection, and non-infectious inflammation.[9] In AeCOPD cases, it is well known the possible role of PCT in addition to CRP, white blood cell (WBC), sputum cultures in the desicion of antimicrobial treatment.[3,5] PCT
may provide clinically relevant information and it may be a guideline for antibiotic treatment. We could not find any report which indicated the role of PCT in prediction of necessity of noninvasive positive pressure ventilation (NPPV) treatment.

In this study, we aimed to examine PCT levels during AeCOPD and stable period of COPD, to evaluate possible usage of PCT in the prediction and the severity of an acute exacerbation and its importance on the planning of NPPV treatment. We also investigated the correlation between PCT levels, and the stage of COPD, arterial blood gas (ABG) analysis, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), WBC, and neutrophil counts.

MATERIALS AND METHODS

In this cross sectional study (2009-2010) 118 consecutive COPD cases were enrolled, 68 of them (58%) were in acute exacerbations (case group), while 50 of them (42%) were stable COPD patients (control group). Diagnoses of COPD were based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. Acute exacerbation was defined with the presence of at least one of the following respiratory symptoms such as deterioration of stable state COPD, increase in the amount and purulency of sputum, gradually worsening dyspnea, and wheezing. Patients without any symptoms of an acute exacerbation at least four weeks were considered cases with stable COPD. Individuals less than 18 years of age, pregnant cases, cases with pulmonary diseases other than COPD (asthma, bronchiectasis, pneumonia, tuberculosis), sepsis, pulmonary and extra pulmonary malignancies and any diseases which cause an increase in serum PCT levels. These subjects were excluded from the study. Also the cases who had received antibiotherapy before our evaluation were not included in our study. The study was approved by Ethics Committee of Gaziosmanpasa University Faculty of Medicine and supported by The Commission of Scientific Research Projects (2009/34). All patients participating in the study gave their written consents.

Postero anterior chest X-ray, hemogram, ESR, ABG (Medica Corp. Bedford, MA, USA), pulmonary function tests (PFTs) (Jager, Master Screen Pneumo), serum CRP ve PCT levels were obtained. Quantitative assessment of PCT was performed using mini VIDAS® (Biormerieux Diagnostic, France) by Enzyme Linked Florescent Assay (ELFA) method and the results were evaluated in the same day. In healthy individuals reference value was determined as <0.05 ng/ml varying slightly with the analytical method used.

For the evaluation of the type of exacerbations, Anthonisen criteria were used. Accordingly, the presence of all of the following criteria such as an increase in the severity of dyspnea, intensity of the purulency, and amount of the sputum were defined as Type 1 exacerbation, while Type 2 exacerbation requires the presence of two of these symptoms. The presence of one of the symptom described previously and upper respiratory tract infection, fever, and an increase in the severity of wheezing and cough, a 20% increase in the respiratory/heart rate within the previous 5 days was defined as Type 3 AeCOPD.

The severity of exacerbations was evaluated according to Turkish Thoracic Society, Guidelines for the Diagnosis and Management of COPD. The cases were evaluated according to the presence of homecare facilities, the absence of cyanosis/impaired consciousness/long term oxygen treatment/damaged daily activities and social conditions. If the patient says ‘yes’ ≥4 of these questions, he/she is determined as mild AeCOPD and they were treated on an ambulatory basis, while moderate/severe cases were hospitalized. Non Invasive Positive Pressure Ventilation (NPPV) therapy was administered for in-patients whose ABG analyses revealed moderate/severe acidosis (pH < 7.35), hypercapnia (PaCO₂ > 45 mmHg) or resistant hypoxemia inspite of nasal oxygen support.

For statistical analysis SPSS (Statistical Package for Social Sciences) Release 18.0 software package program (SPSS, Inc. Chicago, IL) was used. For the comparison of qualitative data, chi-square test was used. Correlations among procedures with measurable outcomes were analysed using Pearson Correlation coefficient. In the comparison of means of measurable variable ‘test for the sigificance of a difference between two means’ was used, in cases where data do not fit into normal distribution Mann Whitney U test which is a non-parametric counterpart of the latter test was employed. For the establishment of PCT cut-off value so as to make a distinction between cases treated with or without NPPV, ROC (Receiver Operating Characteristic) analysis was performed, and area under curve (AUC) was calculated. P values below 0.05 were considered statistically significant.

RESULTS

Totally 118 COPD patients cases were enrolled into the study. Sixty eight of them had AeCOPD (case group) and the others had a stable COPD (control group). The groups were comparable as for mean ages and gender distribution. Demographic, and clinical characteristics of the groups are seen in Table 1.

Fourthy five of 68 (66%) AeCOPD patients were hospitalized and 22 of them treated with NPPV. None of these hospitalized cases were intubated. Patients with mild exacerbation (n = 23) were treated as out patient.
CRP, ESR, WBC, neutrophil (%), and PCT values were significantly higher in the case group [Table 2].

Mean PCT levels were significantly different in terms of type and severity of AeCOPD [Table 3].

PCT levels in 40 (59%) of 68 patients with AeCOPD were higher than normal value (0.05 ng/ml), in 15 cases (22%) PCT levels were higher than 5 fold of normal value (0.25 ng/ml).

PCT cut-off value was defined as 0.07 ng/ml for differentiation of mild and moderate/severe exacerbation, the sensitivity and the selectivity were 82% and 91%, respectively (area under ROC curve = 0.887, confidence interval [CI] 0.804-0.970, P = 0.0001) [Figure 1]. In 3 of 23 hospitalized AeCOPD cases who were not perform NPPV, PCT levels were higher than 0.25 ng/ml. In 12 of the cases who were performed NPPV, PCT levels were higher than 0.25 ng/ml (P = 0.003).

In AeCOPD cases who had indications for hospitalization, mean (SD) PCT levels in those managed with or without NPPV therapy were respectively 0.36 (0.26) ng/ml, and 0.15 (0.16) ng/ml (P = 0.0001) [Figure 2]. ROC analysis was performed to determined the cut-off value of PCT for indication of NPPV treatment and PCT cut-off value was determined higher than 0.1 ng/ml (sensitivity, 95%; selectivity, 78%; area under ROC curve 0.894, CI 0.821-0.967, P = 0.0001) [Figure 3].

Any difference between PCT levels based on stages of COPD was not observed (P = 0.128)

We determined significant negative correlation between PCT levels and pH and pO2, also we detected significant positive correlation between PCT levels and ESR, WBC, neutrophil and CRP in AeCOPD cases.

A strongly positive correlation was detected between the number of acute exacerbations during the previous year, and PCT values measured during acute exacerbations of COPD (r = 0.514, P = 0.0001).

Among in-patients, any association between duration of

![Figure 1: ROC curve, sensitivity, and specificity of PCT cut-off value in mild or moderate/severe exacerbations](image1)

![Figure 2: Mean PCT levels (ng/ml) in patients treated with or without NPPV](image2)

![Figure 3: Mean PCT cut-off value predicting the indication for NPPV, and related ROC curve](image3)

**Table 1: Demographic, and clinical characteristics of the study groups**

| Mean Age (yrs) | Case group (n=68) (%) | Control group (n=50) (%) | P value |
|---------------|----------------------|--------------------------|---------|
| Gender (male/female) | 65.9 (0.97) | 64.1 (1.22) | 0.245 |
| BMI (kg/m²) | 58 (85)/10(14) | 46 (92)/4(8) | 0.266 |
| Smoking history (Packet/year) | 26.6 (0.58) | 26.9 (0.78) | 0.752 |
| Stage of COPD | 46.1 (2.89) | 45 (2.88) | 0.785 |

BMI=Body mass index; COPD=Chronic obstructive pulmonary disease. *Data were presented as mean (standard error of mean)
hospital stay, and levels of PCT ($r = 0.254$, $P = 0.105$) was not detected.

**DISCUSSION**

In this study the mean levels of PCT were found to be higher in AeCOPD patients than in stable COPD patients and in cases with severe AeCOPD than others. According to our results we can say that PCT levels may be used to predict the necessity of NPPV therapy in AeCOPD patients and value of PCT as 0.10 ng/ml may be a cut off as a predictor of necessity of NPPV treatment in these patients.

In Ece et al.’s study, it was reported that PCT levels were higher in AeCOPD patients, than controls who had noninfectious pulmonary diseases. In a study performed by Polzin et al., a difference was observed between AeCOPD patients and stable COPD patients according to PCT levels. Tasci et al. reported same results, too. Our results are compatible with these studies. In the same study a correlation was detected between PCT levels, and ESR, length of hospital stay and purulence of sputum while any association between WBC, and clinical symptoms was revealed. We detected a significant positive correlation between PCT levels during an acute episode, and CRP, ESR, WBC and neutrophil counts. In compliance with our study Daniels et al. reported positive correlation between PCT and CRP.

In another study evaluating 167 AeCOPD cases according to Anthonisen classification, higher levels of CRP were determined in type 1 acute attack than other types. It was also indicated that PCT levels were associated with length of hospital stay. In the same study PCT levels of patients requiring intensive care on admission were also found to relatively higher than others. We determined statistically significant difference according to PCT levels in all types of acute attacks and highest level was determined in type 1. PCT levels were higher in in-patients than out-patients, and among in-patients PCT levels were higher in cases who were underwent NPPV therapy than others. A significant positive correlation between PCT levels and pCO$_2$ was seen, and a negative one between pH, and pO$_2$ was observed.

These findings suggested that PCT levels were associated with severity of respiratory failure in AeCOPD. In our study any correlation between duration of hospital stay, and levels of PCT was not found but Tasci et. al indicated a positive correlation between length of hospital stay and PCT levels.

Among the studies where the association between the stage of COPD, and PCT has been evaluated, Stolz et al. found similar PCT levels in all stages of COPD, while Daubin et al. reported PCT levels of >0.25 µg/L in patients with very severe (FEV$_1$ <30%) COPD. In our study PCT levels in various stages of COPD did not differ. A positive correlation was detected between the number of acute exacerbations within last year, and levels of PCT. This finding indicated that levels of PCT might provide information about frequency of acute exacerbations, and inadequacy of treatment.

Rammaert et al. revealed that higher PCT levels in a severe AeCOPD cases were associated with necessity of mechanic ventilation and intensive care unit mortality. In the same study they reported high mortality rate in cases whose PCT livels higher than 0.24 ng/ml. In another study, the levels of PCT higher than 0.25 µg/L in COPD cases who treated in intensive care unit were found to be related with mortality. Unlike these studies Hurst et al. reports that systemic biomarkers were not helpful in predicting the severity of AeCOPD. In our study, we could not make any prognostic evaluation because of none of the patients did not die during hospitalisation because of AeCOPD. We do not have any data about long term mortality of these cases out of hospital. In 55% of the cases managed with NPPV, PCT levels higher than 0.25 ng/ml were seen, which were significantly higher than others (13%). Besides, PCT cut-off value for indicating the necessity of NPPV was determines as 0.10 ng/ml. This result is important to predict the necessity of NPPV treatment in terms of the PCT level in the first evaluation of COPD patients.
CONCLUSION

We know that our study has the limitation of a relatively small number of patients, particularly when determining cutoff points for PCT levels but in literature we could not find any report which investigated the importance of PCT on the planing of NPPV treatment in AeCOPD patients. We know the fact that the physicians should follow the universally accepted criteria for NPPV in AeCOPD patients and the clinical evaluation and the gas exchange are the main criterias. But PCT which is an important marker in the prediction of infectious episodes of COPD might be a predictor of NPPV treatment necessity. We think that the positive correlation between the levels of PCT and pCO2 which is the main predictor in our clinic to start NPPV treatment shows the compliance of our results with the criterias defined previously for this therapy. Detection of PCT levels higher than 0.10 ng/ml in a AeCOPD patient could alert us to think the necessity of NPPV.

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