Original Article

Procalcitonin as a Diagnostic Marker in Patients of Acute Bacterial Exacerbation of Chronic Obstructive Pulmonary Disease

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Abstract

Objective. Common factors for exacerbation of chronic obstructive pulmonary disease (COPD) are viral and bacterial infections. Presence of purulent sputum for the initiation of antibiotic therapy is non judicious because antibiotic usage in viral exacerbation may lead to the development of bacterial resistance and unnecessary economic burden on the patient. Procalcitonin (PCT) is a marker which can be used to differentiate between viral and bacterial causes as an aetiology of these exacerbations.

Methods. Patients with exacerbation of COPD (increased dyspnoea, cough, increased sputum volume and/or purulence) were identified. Sputum culture was sent along with serum PCT levels. Patients were divided into two groups – Group I (COPD patients with bacterial exacerbation, confirmed by the sputum culture) and Group II (COPD patients without bacterial exacerbation). Serum PCT levels were measured in both the groups.

Results. Results of the study revealed that PCT levels ranged from 0.01 to and 12.03 ng/mL with a mean value of 3.18±2.60 ng/mL in Group I and 0.23±0.39 ng/mL in Group II and median values of 2.98 ng/mL in Group I and 0.09 ng/mL in Group II. There was a statistically significant difference between the two groups (P<0.001) with Group I showing a higher mean values compared to Group II. A significant near strong correlation was observed between total leucocyte count and PCT levels (r=0.699; P<0.001). However, a weak negative and borderline significant correlation between forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) levels and PCT levels was observed (r=–0.199; P=0.050).

Conclusion. Procalcitionin can be used to differentiate between bacterial and viral exacerbation of COPD. PCT- guided antibiotic therapy has a potential to decrease the unnecessary use of antibiotics and economic burden on the patient.
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Key words: COPD, Procalcitonin, Acute bacterial exacerbation

Introduction

Chronic obstructive pulmonary disease (COPD) is a major health problem and is the fourth leading cause of death in the world, leading to substantial economical and social burden.[1] According to World Health Organization (WHO) estimates, 6.5 crore people have moderate to severe COPD in the world. More than 30 lakh people died of COPD in 2005 corresponding to 5% of all deaths globally and it may be the third leading cause of death by 2030[2]. There are approximately three crore COPD patients in India.[3] Although cigarette smoking is the best studied factor, non-smoker COPD is also on the rise[4]. Indoor and outdoor air pollutions, occupational exposure, cow-dung and biomass fuel exposure are other important risk factors. Other less frequent causes include genetic factors, lung developmental anomalies, low socio-economic status, and bronchial hyper-reactiveness.

An exacerbation of COPD is defined as an acute event that is characterised by a worsening of the patient's respiratory symptoms from more than normal day-to-day variations and leads to a change in the medications.[5] Each exacerbation accelerates the rate of decline of the lung function[6] which negatively affects the patient's quality of life, and therefore, exacerbation needs to be managed appropriately. Common factors for acute exacerbation of COPD (AECOPD) are viral and bacterial infections and approximately one-third causes of exacerbation remains unknown[7]. Air pollution can also precipitate an exacerbation.[7]

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Presence of purulent sputum for the initiation of antibiotic therapy is inappropriate because the non-judicious use of antibiotic therapy in viral exacerbations may lead to the development of bacterial resistance.[8] Various markers of inflammation, like the C-reactive protein (CRP) and total leucocyte count (TLC) does not accurately differentiate between viral and bacterial exacerbations of COPD. Thus, new reliable diagnostic markers are required.

Procalcitonin (PCT), a 116-amino-acid residue with a molecular weight of 13 kDa, a serum marker, increases the response to bacterial infections, but remains low in non-bacterial infections and other pro-inflammatory conditions.[9] The exact sites of its secretion are unclear.[10] There are various hypothesis those suggest that PCT is secreted from neuroendocrine cells of the liver, small intestine and thyroid cells. In healthy humans, its normal serum level is 0.1 ng/mL. PCT levels start rising two hours after the infection, reaches a peak value 12 hours[11], and remains constant for another 12 hours. The release of PCT is mediated by microbial endotoxins and/or indirectly by humoral factors or the cell-mediated host response.[12] Cytokines released during viral infection attenuate the release of PCT.[10] Therefore, circulating levels of PCT are markedly elevated in patients with bacterial infections compared to those with viral infections or other inflammatory conditions.[13]

The present study was undertaken to investigate the role of PCT in differentiating bacterial from non-bacterial infectious causes of AECOPD, and thereby, in making appropriate decision regarding the use of antibiotics in the management of these patients.

Material and Methods

The present study was conducted in the Department of Respiratory Medicine, King George's Medical University, Lucknow. Ninety-eight patients with COPD were included in the study after a written informed consent. Patients with COPD presenting with symptoms of increased cough and sputum production, increased shortness of breath, high fever were considered to have an acute exacerbation and were included as the study group. Patients with COPD who received antibiotics earlier were excluded from the study. Patients on any type of antioxidant therapy, patients with other chronic illnesses, like chronic kidney disease, diabetes mellitus and cardiomyopahties, pregnancy or lactation with COPD, malignancy, and pulmonary tuberculosis were also excluded from the study.

A diagnosis of COPD was established on the basis of largely irreversible airway obstruction, with <12% improvement in forced expiratory volume in one second (FEV_1) after the inhalation of 200μg salbutamol. The clinical severity of COPD was determined as per the criteria defined in Global Initiative for Chronic Obstructive Pulmonary Diseases (GOLD) guidelines.

All patients underwent detailed history and clinical evaluation. Chest radiograph, spirometry and routine blood investigations were done in all the study patients. Procalcitonin was measured in blood. Sputum culture and Gram stain (sputum was induced with hypertonic saline if patients were unable to expectorate an adequate sputum sample spontaneously) was also done. Sputum specimens were considered adequate by standard criteria of >25 polymorphonuclear leucocytes and <10 epithelial cells per high power-field and were considered positive, if colony forming unit was >105. The blood collected for serum PCT measurement was centrifuged and kept at -80 °C until the time of the measurement.

Patients were divided into two groups; Group I (COPD patients with bacterial exacerbation, confirmed by sputum culture) and Group II (COPD patients without bacterial exacerbation). Serum PCT levels were measured in both the groups.

Statistical Analysis

The statistical analysis was done using Statistical Package for Social Sciences (SPSS version 15.0) and the values were expressed in number (%) and mean±SD (Standard deviation). The significance of the two means was tested using the student 't' test.The value of Pearson's correlation coefficient ranges from –1 to +1 with +1, indicating perfect positive correlation and –1 indicating perfect negative correlation. A P-value of <0.05 was considered significant.

Results

Out of a total of 98 patients, 51 (52%) were COPD patients with bacterial exacerbation (Group I) and remaining 47 (48%) were COPD patients without bacterial exacerbation (Group II). The mean haemoglobin levels were 11.1±2.0 g/dL in Group I and 11.8±1.2 g/dL in Group II (P=0.055; t=–1.945). The TLC was 9.8±3.1/μL in Group I and 8.4±1.6 /μL in Group II. The difference was significant statistically (t=2.782; P=0.007).

Both pre- and post-bronchodilator pulmonary efficiency as well as vital capacity parameters were significantly higher in Group I as compared to Group II (p<0.05). Post-bronchodilator FEV_1/FVC ratios also showed a similar trend with mean values in Group I and II to be 48.82±9.58 and 54.14±8.88, respectively; thus showing a significant inter-group difference (p=0.006) (Table 1).

Table 1. pre- and post-bronchodilator pulmonary functions in both the groups

Parameters	Group I (N=51) (Mean±SD)	Group II (N=47) (Mean±SD)	Statistical Significance 'T'	'P'
Pre FEV_1	0.70±0.33	0.87±0.37	-2.303	0.023
Pre FVC	1.39±0.54	1.67±0.53	-2.596	0.011
Post FEV_1	0.75±0.33	0.97±0.39	-2.989	0.004
Post FVC	1.54±0.55	1.87±0.58	-2.865	0.005
Post FEV_1 / FVC (%)	48.82±9.58	54.14±8.88	-2.839	0.006

Definition of abbreviations: SD=Standard deviation; FEV_1=Forced expiratory volume in one second, FVC=Forced vital capacity.

Mean PCT levels in Group 1 were 3.18±2.60 ng/mL (range 0.05–12.03) and 0.23±0.39 ng/mL in Group II (range 0.05–1.85) (t=7.709; P<0.001). median values in Group I and II were 2.98ng/mL and 0.09ng/mL, respectively. We observed a significant statistical difference between the groups (p<0.001) with Group I showing a higher mean value as compared to Group II (Table 2).

The overall correlation of PCT levels with TLC levels and post-bronchodilator FEV_1/FVC ratio is shown in figure 1A. A significant near strong correlation was observed between TLC levels and serum PCT levels (r=0.699; p<0.001). However, a weak negative and borderline significant correlation between FEV_1/FVC and PCT levels was observed (r=–0.199; P=0.050) (Figure 1B). On evaluating the correlation of PCT levels with TLC and FEV_1/FVC levels in independent groups, significant correlation was observed in Group I only where a strong positive correlation between TLC and PCT levels was observed (r=0.772; P<0.001) (Table 2). All the other correlations did not yield a significant association (Table 2).

Discussion

Infection is a major cause of mortality and morbidity in patients with COPD. There may be a wide variety of pathogens (most commonly viral and bacterial) resulting in AECOPD. The choice to use antibiotics to treat an exacerbation episode is a clinical decision. Recently, use of PCT to guide antibiotic therapy has significantly reduced the injudicious use of antibiotics without compromising the patient's outcome as shown in various randomised controlled trials.[13,14]

In the present study, the levels of PCT for Group I patients with bacterial COPD exacerbations were significantly higher than Group II with non-bacterial COPD exacerbations (P<0.001). Our results are in consionance with a study by Chang *et al*[15] that showed that patients admitted with COPD exacerbations and

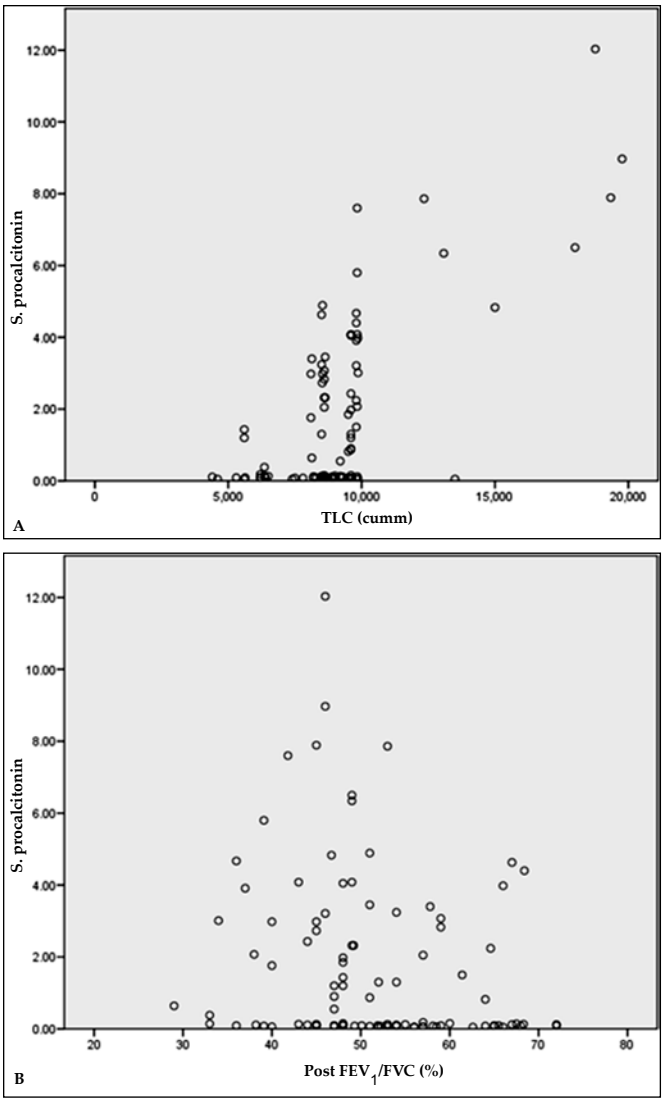

Figure 1. Correlation of prolactin levels (A) with TLC and (B) post-bronchodilator FEV_1/FVC ratio.

Table 2. Correlation of prolactin levels with TLC and FEV_1/FVC in both the groups

Correlation of Procalcitonin Levels with	No. of Pairs	'r'	'P'
Group I			
TLC	51	0.772	<0.001
FEV_1/FVC	51	-0.032	0.825
Group II			
TLC	47	0.259	0.079
FEV_1/FVC	47	0.081	0.079

Definition of abbreviations: TLC=Total lung capacity; FEV_1=orced expiratory volume in one second; FVC=Forced vital capacity.

positive sputum cultures for bacterial pathogen had significantly higher PCT values. Various other studies observed that the levels of circulating PCT increased in severe bacterial infections, but remains low in viral infections.[10] We found that a high PCT level was relatively specific for invasive bacterial disease such as pneumonia, that is in contrast with their European studies.

Acquisition of new strains of pathogen rather than their load appears to be the most important factor in the pathogenesis of AECOPD. Our study observed that PCT has a significant correlation with leucocyte count and when these parameters are used in combination, it increases the predictive value in identifying the bacterial infection.

In the present study, a significant correlation was found between the PCT level and FEV_1 in COPD exacerbations of bacterial aetiology indicating that high PCT may point to an increase in severity of AECOPD. This is in agreement with a recent study[16], where 19 patients with AECOPD and 16 patients with stable COPD as the control group were included and it was concluded that the mean serum PCT levels in COPD patients with exacerbations was 1.8ng/mL and 0.2ng/mL in stable COPD patients.

Results of our study are in conformity with other studies by Lacoma *et al*[17] and Bafadhel *et al*[18] those reported that PCT can be used to differentiate between bacterial and viral causes of AECOPD.

There are some limitations in the present study as we did not have a healthy control group and did not compare the levels of PCT in non-COPD patients.

Conclusions

The present study demonstrates that procalcitonin can be as a useful marker to guide initiation and assessing response to antibiotic therapy in AECOPD to differentiate between bacterial and non-bacterial causes of the exacerbation. Procalcitonin-guided antibiotic therapy has the potential to decrease unnecessary antibiotic usage in non-bacterial COPD exacerbations, thereby decreasing the development of antimicrobial resistance and reducing health-care costs in our country.

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