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Research Article

PROCALCITONIN AS A GUIDE FOR ANTIBIOTIC THERAPY IN PATIENTS ADMITTED WITH ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable, but progressive disease and hospital admissions of patients with COPD are frequently due to acute exacerbations. Recently, measurement of procalcitonin (PCT) levels appears to be useful in order to minimize this problem as acute phase reactants does not difference between bacterial and non-bacterial causes of inflammation.

Aim; The aim of this study was to investigate whether the measurement of Procalcitonin can be used in the differentiation of bacterial and non-bacterial infectious causes of COPD exacerbation, thus helping in planning the treatment, reduce overuse of antibiotics in patients admitted with acute exacerbation of COPD thus reducing economic burden and decrease drug resistance. 86 patients with known COPD and admitted in emergency department with symptoms of acute exacerbation of COPD were included in this study after obtaining written informed consent. At presentation before putting antibiotics blood samples were taken for procalcitonin level, routine blood tests including sputum and blood culture. Patients were allocated in to three groups based on procalcitonin value.

Group A; procalcitonin value below < 0.25 ng/ml. (normal) (n=57)

Group B; procalcitonin value between 0.25- 0.5 ng/ml (local bacterial infection) (n=8)

Group C; procalcitonin value between 0.5-2 ng/ml (systemic bacterial infection) (n=21)

Results ; In our study a correlation was seen between procalcitonin value in each group and WBC count, fever, ESR, CRP, Vaccination, Chest X ray, smoking and microbiology i.e. blood and sputum culture. A significant correlation was seen between serum procalcitonin value and WBCCount, fever, chest x ray, CRP, blood and sputum culture. (P valve $\leq$ 0.0001) but no significant correlation was seen between serum procalcitonin level in each group with ESR which is one of acute phase reactant p valve 0.043

Conclusions: This study demonstrates that procalcitonin is a good marker for differentiation between bacterial and nonbacterial acute exacerbation of COPD and could be used to guide initiation and assessing response to antibiotic therapy in patients. Procalcitonin- guided antibiotic therapy has the potential to decrease unnecessary antibiotic use in nonbacterial COPD exacerbations, thereby decreasing the spread of antibiotic-resistant bacteria and reducing antibiotic-related adverse reactions.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a preventable as well as treatable disease that might also have extra-pulmonary manifestations. It is characterized by an abnormal inflammatory response of the lungs against harmful particles or gases (1) COPD constitutes a major health problem [2]. Acute exacerbations of COPD (AECOPD) have considerable impact on morbidity, mortality and quality of life [3] An exacerbation of COPD is an event in the natural course

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of COPD characterised by an acute change in the patient's baseline dyspnoea or breathing difficulty, cough and/or sputum production beyond day-to-day variability sufficient to warrant a change in management (Gold definition) [4] . It is essential to determine the cause of worsening of symptoms for appropriate clinical management. The available evidence suggests that at least 80% of the COPD exacerbations are infectious in origin. Of these infections, 40% to 50% are caused by bacteria, 30% by viruses, and 5% to 10% by atypical bacteria [5-15] The role of bacteria in exacerbations has not been established with reasonable certainty since bacterial species are present in the airways of 25%–50% patients with COPD even in stable conditions [16-19] While there is well- established evidence for the use of steroids and bronchodilators in acute exacerbation of COPD, the debate continues over the appropriate use of antibiotics in the treatment of acute exacerbations. There are multiple potential factors leading to acute exacerbation of COPD, including viruses, bacteria, and common pollutants; as such, antibiotic treatment may not be indicated for all patients presenting with exacerbations. Further, the risks of antibiotic treatment-including adverse drug events, selection for drug-resistant bacteria, and associated costs-are not insignificant. Classical diagnostic parameters including CRP and leukocyte count do not have sufficient specificity in differentiating between bacterial infections, non-infectious systemic inflammations or viral infections. Therefore, more specific and reliable markers that might be helpful in deciding the treatment are needed in these patients [20]. Serum procalcitonin levels are suggested to be one of the biomarkers for predicting a bacterial infection [21]. Procalcitonin (PCT) is a protein having a molecular weight of 13 kDa and it consists of 116 amino acid residues. The exact regions of its secretion are not yet clear [22].

Some literature suggests 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. In a previous study, administration of bacterial endotoxin to healthy Individuals resulted in an increase in PCT levels starting two hours after administration, with a peak value reached in 12 h [23]. Consequently, the serum level remains constant for another12 h and decreases back to normal level in 20–24 h.PCT gives rapid response to bacterial infections [24]. Studies performed in patients with pneumonia revealed that serum PCT levels have high sensitivity and specificity in showing the inflammatory response caused by pneumonia [25]. It has also been suggested in some studies that serum PCT levels might have a relatively higher sensitivity and specificity in differentiating pneumonias of bacterial origin from those of viralorigin [26].

Aim

The aim of this study was to investigate whether the measurement of PCT can be used in the differentiation of bacterial and non-bacterial infection causes of COPD exacerbation, thus helping in planning the treatment.

MATERIAL AND METHODS

Between November 2012 and April 2014 86 patients (47 males and 39 females) with known copd and admitted in emergency department with symptoms of acute exacerbation of COPD (worsenening of cough, increased sputum production, increased breathlessness) were included in this prospective study after taking written informed consent.

Inclusion Criteria were patients of age 18 who were already diagnostic cases of COPD [Gold criteria, PFT documented] and have not received antibiotics in last 2 weeks nor have been hospitalized in last 2 weeks. Exclusion Criteria were Age< 18 years, Pregnant women, Patients with absolute neutropenia and Immunocomprised patients.

Definition

The diagnosis of COPD was based on clinical history, physical examination findings, and spirometric criteria according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [14]. An exacerbation of COPD was defined as ''a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD[15].

METHODS

Complete medical history.

- General and local chest examination.
- Chest radiography.
- Routine blood tests (including CBC, ESR and CRP).
- Blood cultures, sputum culture (Sputum was induced with hypertonic saline if subjects were unable to expectorate an adequate sputum sample spontaneously).

Procalcitonin level by ELISA method

OBSERVATIONS AND RESULTS

Characteristics of subjects with acute exacerbation of COPD stratified by procalcitonin value above and below threshold i.e 0.25 ng/ml are summarized in table I

In our study we observed potential correlation of Procalcitonin value in each group with clinical parameters like WBC count, fever, ESR, CRP, Vaccination, Chest X ray and microbiological parameter blood and sputum culture.

A significant correlation was seen between procalcitonin value and WBC count as showing in table 1 with p value ≤ 0.001 between various groups. There is also significant corelation noted between procalcitonin valve and chest x ray as described in table 1 with p value ≤ 0.001. A significant correlation was also noted between patients who were smokers and procalcitonin level with p value 0.0019. When procalcitonin level was correlated with CRP level (it was found that among 57 patients with normal Procalcitonin level i.e. < 0.25ng/ml (Group A) CRP was positive in only 14 patients (24.6%) whereas among 8 patients in group B with high Procalcitonin value (0.25-0.5ng/ml) and among 21 patients in group C (Pct. value >0.5ng/ml) CRP was positive in 4(50%) patients and 17 (80.9%) respectively which is statistically significant p value <0.001. However there was no significant correlation seen between procalcitonin value in each group and ESR with p value 0.43, A significant correlation was also seen between procalcitonin valve and fever (p valve≤ 0.001ng/ml) However there was no significant correlation between Pct. valve and

vaccination p value 0.133, A significant correlation was seen between procalcitonin value and blood culture.

Patients in group A blood culture was positive in only 4 patients(7%) where as in patients of group B(n= 8) with local bacterial infections blood culture was positive in all 8 patients(100%) and in patients of group C with systemic bacterial infection blood culture was positive in 16 patients (76.2%). P value ≤ 0.001. A significant correlation was also seen between procalcitonin value and sputum culture In group A patients sputum culture was positive in only 3 patients (5.3%) where as in group B patients with local bacterial infections sputum culture was positive in 3 patients (37.5%) and in group C patients with systemic bacterial infection (pct >0.5ng/ml) sputum culture was positive in 12 patients (57.1%) which is statistically significant.(p value 0.001)

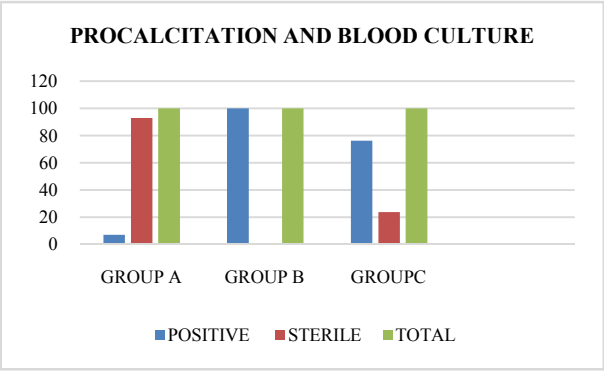
Table No 1 Showing Characteristic Features of Various Groups

Characteristic	GROUP A Pct ≤ 0.25 ng/ml N 57	GROUP B Pct 0.25-0.50 ng/ml N 8	GROUP C ≥ 0.5ng/ml N 21	P valve ng/ml
Age (mean±s.d)	65.02 ± 10.05	58.75± 7.4	61.8± 6.8	0.118
TLC COUNT(mean±s.d)	8.69 ± 2.5	12.2 ± 3.2	12.1 ± 3.8	≤0.001
E.S.R (Mean± s.d)	17.02 ± 8.7	23.13± 7.2	21.6 ±9.0	0.43
C.R.P (POSITIVE)	14	4	17	≤0.001
Chest x ray infiltrates	15	6	17	≤0.001
Smoker	23	6	15	0.0019
Vaccinated Influenza	0	1	2	0.133
Pneumococcal	5	1	0	
Both influenza and pneumococcal	3	0	0	
Fever	20	2	19	≤0.001
Positive sputum culture	3	3	12	≤0.001
Positive blood culture	4	8	16	≤0.001

Table 2 Correlation between procalcitonin and blood culture

Procalcitonin(ng/ml)	Sterile	Positive	Total
Group A(Procalcitonin value i.e< 0.25ng/ml)	93.0%	7.0%	100.0%
Group B(procalcitonin value between 0.25- 0.5 ng/ml)	100.0%	0.0%	100.0%
Group C (procalcitonin value between 0.5-2 ng/ml)	0%	100%	100.0%

The 2 showing that there is significant increase in blood culture positivity rate with higher procalcitonin level in Group C with 76.2% than in Group A with only 7 % (p≤0.001)



The above table 4 shows significant relation between procalcitonin level with sputum culture with highest percentage of positive culture in group C and p valve ≤0.001

Table 3 Showing Various Bacteria Growth in Culture and Relation With Procalcitonin

Blood culture organism	Procalcitonin(ng/ml)			Total
	Group A	Group B	Group C	
No organism	93.0%	100.0%	23.8%	76.7%
Klebsiella	0.0%	0.0%	19.0%	4.7%
Acinetobacter	0.0%	o.o%	4.8%	1.2%
Streptococcus	1.8%	0.0%	4.8%	2.3%
Pseudomonas	1.8%	0.0%	9.5%	3.5%
Candida	0.0%	0.0%	4.8%	1.2%
Coaglase negative stap aureus	0.O%	0.0%	9.5%	2.3%
Enterococcus	1.8%	0.0%	4.8%	2.3%
MRSA	0.0%	0.0%	14.3%	3.5%
Staph aureus	1.8%	0.0%	4.8%	2.3%

Table 4 Correlation between procalcitonin and sputum culture

Procalcitonin(ng/ml)	Sputum culture Sterile	Sputum culture Positive	Total
Group A(Procalcitonin value i.e.< 0.25ng/ml)	94.7 %	5.3 %	100.0%
Group B(procalcitonin value between 0.25- 0.5 ng/ml)	62.5 %	37.5%	100.0%
Group C procalcitonin value between 0.5-2 ng/ml)	42.9%	57.1.2%	100.0%

Table 5 Showing Sputum culture 0rganism and serum procalcitonin (ng/ml) level

Sputum culture organism	Procalcitonin(ng/ml)			Total
No organism	Group A	Group B	Group C	79.1%
Klebsiella	1.8%	0.0%	23.8%	4.7%
Acinetobacter	0.0%	12.5%	9.5%	1.2%
Streptococcus	1.8%	12.5%	0.0%	2.3%
Pseudomonas	0.0%	12.5%	9.5%	3.5%
Candida	0.0%	0.0%	4.8%	1.2%
Coaglase negative stap aureus	0.O%	1.0%	9.5%	2.3%
Enterococcus	1.8%	0.0%	4.8%	2.3%
MRSA	0.0%	0.0%	4.3%	3.5%
Staph aureus	1.8%	1.0%	4.8%	2.3%

DISCUSSION

Procalcitonin levels are increased in moderate to severe bacterial infections but remain at comparatively low levels in viral infections and nonspecific inflammatory diseases [27].There are only a limited number of studies investigating the diagnostic role of procalcitonin in invasive fungal infections. However, these studies were inconclusive because of limited sample size and different procalcitonin cut off values employed [28] This is the first study in the Kashmir valley to examine the utility of procalcitonin levels in patients with COPD, and consistent with the European literature, we found that a high procalcitonin level was relatively specific for invasive bacterial disease such as pneumonia.[29, 30]. In our study we classified patients into three groups:-

Group A with normal procalcitonin level ≤ 0.25ng/ml Group B with procalcitonin level between 0.25ngml-0.5ng/ml. (local bacterial infection). Infection which does not affect whole body of individual, Rather, it is limited to specific portion of body and does not affect the blood stream. e.g, infected wound, thrombophlebitis, gonorrhoea. Sometimes a pneumonia can be localized infection, as it is only located in one specific place in the lung.

Group C with systemic bacterial infection (Procalcitonin level≥ 0.5/ml). A systemic bacterial infection is so named because the

pathogen that causes it, and often the symptoms that it causes, are spread through the systems of body, instead of being localized in one area, as they are in local infection.

In our study we correlate procalcitonin values in each group with higher temperature, white blood cell count, CRP, ESR, chest radiograph, bacteriology in sputum and blood culture, suggesting the possibility of occult pneumonia.

In this study we demonstrate a strong correlation of pct valve with, WBC count, CRP and x ray findings. (p valve ≤ 0.0001) which is in consistent with study conducted by K.H. Mohamed *et al* where significant correlation was seen between PCT level and temperature (pct<0.05), leukocyte count (p<0.05), CRP (P<0.05) but in our study we don't find strong correlation of pct valve and ESR which is against same study [31]. Our study is also in agreement with study Conducted by CanturkTasci *et al* (2008) where they have found strong correlation of pct valve with temperature, CRP, leucocyte count, temperature, Blood culture and x ray infiltrates, a similar result was found in our study but in Our study we do not found strong correlation of pct valve and ESR which is against same study. [32] Chang *et al*. (33) showed that patients admitted with COPD exacerbation and positive sputum cultures for bacterial pathogen ha significantly higher PCT values. A similar result was found in another study of the same investigator performed in2006 [34] A similar result was found in our study. In our study we found that pct valve is strongly correlated with sputum culture and blood culture. Based on our data, low serum procalcitonin concentrations of $\leq 0{\cdot}25$ ng/l can identify patients without clinically relevant bacterial infections; in these individuals antimicrobial therapy can be safely withheld. Our study had several limitations. The number of patients with documented bacterial infection was relatively small. Second limitation of our study is that our findings are based on single measurement and sequential testing might improve the diagnostic value of procalcitonin. Third we did not test for viruses, common pathogens in this population, although this omission does not invalidate the findings for those patients with a viral or bacterial infection identified.

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