The Effect of CRP and Procalcitonin Levels on the Estimation of Infection in the COPD Patients Admitted to ICU with Respiratory Failure

Solunum Yetmezliği ile Yoğun Bakıma Yatırılan KOAH Hastalarında Infeksiyonu Değerlendirmede CRP ve Prokalsitoninin Etkisi

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ABSTRACT Objective: Acute respiratory failure is one of the most frequent reason for ICU admittance of patients with COPD exacerbation. Those patients almost always receive antimicrobial treatment in ICU. Unnecessary antibiotic usage causes increase in antibiotic resistance, excess hospital charge and undesirable side effects. In this study we aimed to investigate the effect of CRP and procalcitonin levels on decision of antimicrobial therapy in patients with COPD exacerbation. Mate**rial and Methods:** Twenty four patients who were admitted to ICU with acute respiratory failure after COPD exacerbation were examined. C-reactive protein, procalcitonin, CPIS and CURB-65 scores were assessed for each patient at the time of admittance to ICU. Microbial culture of tracheal secretions, urine, and blood samples were done routinely as well. According to the results of antibiogram tests, patients received antimicrobial treatment. However if there was a suspicion of the infective disease such as fever (>40°C, <35°C), leukocytosis (>30000), leukopenia (<4000), new radiological infiltration, etc., empiric antibiotic treatment was given to the patients. **Results:** Patients with microbial culture positive results showed significantly higher levels of CRP and procalcitonin than patients with microbial culture negative results. CPIS and CURB-65 scores were comparable with the CRP and procalcitonin levels. After antimicrobial treatment, CRP and procalcitonin levels were decreased in patients both treated according to antibiogram and treated empirically, however it was statistically significant only in the cases treated according to antibiogram. **Conclusion:** According to this study, the initiation of antimicrobial therapy may be manipulated by the levels of CRP and procalcitonin. Antibiotherapy might be considered in patients with microbial culture positive results instead of giving it to every patient admitted to ICU.

Key Words: Procalcitonin;C-reactive protein; pulmonary disease, chronic obstructive

ÖZET Amaç: KOAH alevlenmesi ile hastaneye başvuran hastaların önemli bir bölümü akut solunum yetmezliği ile yoğun bakım ünitesine (YBÜ) sevkedilmektedir. Bu hastaların hemen tamamı YBÜ'de antimikrobiyal tedavi almaktadır. Uygun olmayan antibiyotik kullanımı hastane yatış maliyetini, antibiyotiklere direnci ve yan etki görülme olasılığını artırmaktadır. Bu çalışmada C-reactive protein (CRP) ve prokalsitonin seviyelerinin KOAH alevlenmesi hastalarında uygulanacak antimikrobial tedavi kararı üzerindeki etkisini araştırmayı amaçladık. **Gereç ve Yöntemler:** KOAH alevlenmesi sonrası akut solunum yetmezliği ile YBÜ'ne yatırılan 24 hasta incelendi. YBÜ'e gelen her hastanın CRP ve prokalsitonin seviyeleri, CPIS ve CURB-65 skorları ölçüldü. Rutin olarak her hastanın trakeal sekresyon, idrar ve kan örneklerinin kültürleri yapıldı. Antibiyogram test sonuçlarına göre hastalara antibiyotik tedavisi verildi. Ancak ateş (>40°C, <35°C), lökositoz (>30000), lökopeni (< 4000), vb. gibi infeksiyon şüphesi olduğunda ampirik olarak antibiyoterapi başlandı. **Bulgular:** Kültür pozitif olan hastalarda CRP ve prokalsitonin seviyeleri kültür negatif hastalara göre anlamlı olarak daha yüksekti. CPIS ve CURB-65 skorları CRP ve prokalsitonin seviyeleri ile uyumlu idi. Antibiyotik tedavisinden sonra, CRP ve prokalsitonin seviyeleri hem ampirik tedavi grubunda hem de kültür pozitif grubunda azaldı, ancak sadece kültür pozitif grubunda istatistiksel olarak anlamlı idi. **Sonuç:** Bu çalışmaya göre CRP ve prokalsitonin seviyeleri antimikrobiyal tedavi kararını vermede yönlendirici olabilir. Antibiyoterapinin YBÜ'e yatan her hasta yerine sadece kültür pozitif hastalara verilmesi uygun olacaktır.

Anahtar Kelimeler: Prokalsitonin; C-reaktif protein; kronik obstrüktif akciğer hastalığı

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Chronic obstructive pulmonary disease (COPD) is seen frequently throughout the world. Exacerbations are the major cause of morbidity and mortality in patients with COPD and associated with impaired quality of life, decline in lung function and poorer outcome.[1] Most of these COPD cases with acute exacerbations are referred to intensive care unit (ICU) and 26-74% patients are intubated.[2] Viral infections are mainly responsible for the exacerbation, synergistic effect of viral and bacterial infections is also important. However, almost all patients in ICU receive antibiotic therapy empirically due to difficulty in definitive determination of an infectious cause of COPD exacerbation. In fact adequate antibiotic treatment was defined as coverage of all pathogens isolated, and determined by the sensitivity pattern in the antibiogram.[3] Besides, conditions other than respiratory infections, including industrial pollutants, allergens, sedatives, congestive heart failure, and pulmonary embolism, have been identified as well.[4,5] Discrimination of the causes of acute exacerbation of COPD is important in order to manage the treatment. It has been demonstrated that bacterial exacerbation was associated with significantly greater neutrophilic inflammation than nonbacterial exacerbation, with higher levels of inflammatory markers.[6] C-reactive protein (CRP) is an acute-phase reactant with well-documented sensitivity that is commonly used to diagnose infectious and inflammatory conditions, including COPD exacerbation.[7,8] Circulating levels of procalcitonin (PCT) are markedly elevated in patients with bacterial infections compared to those with viral infections or other inflammatory conditions.[9] It has been indicated that guidance with the measurement of procalcitonin levels reduces the exposure of patients to antibiotics after presentation to the emergency department for exacerbations of COPD.[10] Unnecessary antibiotic usage causes increase in antibiotic resistance, excess hospital charge and undesirable side effects. In this study, we aimed to investigate the effect of CRP and procalcitonin levels on decision of antimicrobial therapy, the correlation of CRP and procalcitonin levels with the clinical pulmonary infection score (CPIS)[11] and CURB-65 (confusion, urea >7 mmol/L, respiratory rate 30/min, low blood pressure, and age 65 yrs)[12] score in those defined patients.[13,14]

MATERIALS AND METHODS

The study was conducted in the intensive care unit ofBilim University Medical School Avrupa Florence Nightingale Hospital. Twenty four patients (15 female, 9 male) who were admitted to ICU with a diagnosis of acute respiratory failure after COPD exacerbation were examined retrospectively after the approval by the ethical committee of the local medical faculty. 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] All patients needed mechanical ventilation and they intubated orotracheally. Indications for invasive mechanical ventilation were severe dyspnea with use of accesory muscles and paradoxical abdominal motion; respiratory frequency >35 breaths/minute, severe acidosis (pH <7.25) and/or hypercapnia (PaCO2 >60 mmHg); life threatening hypoxemia; and unable to tolerate NIV according to GOLD criteria.[16] Exclusion criteria were coexistence of TB infection or lung cancer, and use of chronic oral or parenteral steroids. CPIS ve CURB-65 scores were calculated at the time of admittance to ICU and chest X-ray, arterial blood gases, complete blood count, BUN, creatinine, total bilirubin, albumin, sodium, potassium, chloride, CRP, PCT were obtained and repeated on the fourth and fourteenth day. CRP was measured by BPC BIOSED Prime-photometer, Italy. Procalcitonin was measured using 20 to 50 µL of plasma or serum by a time-resolved amplified cryptate emission technology assay (PCT Kryptor; BRAHMS). Microbiologic culture of tracheal aspiration, blood, nasal smear and urine were done routinely. Pathogen isolation achieved patients (culture positive group) received antibiotic treatment according to antibiogram, and patients with no isolated pathogens (culture negative group) received empirical treatment depending on suspicion of infection such as hyper or hypothermia (<35 °C

or >38°C), leukocytosis (>30.000) or leukopenia (<2.000), and infiltration on chest X-ray. Others have not taken any antibiotic therapy.

STATISTICAL ANALYSIS

Analyses were performed using a statistical software package. Discrete variables are expressed as counts (percentages) and continuous variables as mean ± SD or median (range). Mann-Whitney U and Wilcoxon W tests were used for the comparison of CRP and PCT levels between the groups, before and after treatment. All tests were two-tailed; $p< 0.05$ was defined as being significant.

RESULTS

The mean age of the patients was 79.08 ± 11.05. The overall ventilation ranged from 2 to 11 days (median 5 days). None of the patients was current smoker. Patients were classified into three groups: Group 1 included patients receiving appropriate antibiotic treatment according to the results of antibiogram; Group 2 patients had empiric antibiotic treatment in spite of negative microbiologic examination; and Group 3 patients were not treated with antibiotic because of negative results. Patient characteristics are presented in Table 1.

The microbial agents isolated from the various specimens obtained from group 1 patients are listed in Table 2.

Mean score of CPIS in all patients was 2.71 (1.37) and CURB-65 was 1.92 (0.78). Group 1 showed significantly higher levels of CURB-65 and CPIS scores than patients with no pathogen isola-

TABLE 1: Patient characteristics according to the groups.

Parameter	Group 1 (n= 12)	Group 2 (n= 3)	Group 3 (n= 9)	p
Age (years)*	78.75 (11.94)	80 (15.71)	79.12 (10.46)	NS
Gender (male) %	33	33	33	NS
Smoking (>50 pack/year) %	42	40	38	NS
CPIS score*				
1st day	3.38 (1.32)	2.51 (0.57)	1.6 (0.91)	<0.05‡
4th day	2.72 (1.02)	1.99 (1.12)	1.0 (0.85)	<0.05‡
14th day	1.2 (0.96)	1.21 (1.03)	0.66 (0.51)	NS‡
CURB-65 score*				
1st day	2.23 (0.59)	1.66 (0.57)	1.37 (0.51)	<0.05‡
4th day	1.17 (0.98)	1.2 (0.4)	1.01 (0.56)	NS‡
14th day	0.5 (0.12)	0.46 (0.21)	0.35 (0.11)	NS‡

*Results are given as mean ± SD. ‡Group 1vs Groups 2-3. CPIS; clinical pulmonary infection score, ≤6 = low-intermediate probability, >6 = high probability. CURB-65; severity score for community acquired pneumonia, Confusion, Urea nitrogen, Respiratory rate, Blood pressure, 65 years of age and older, 0= very low risk of death, 1-2= increased risk of death, 3-4= high risk of death.

TABLE 2: Microbial etiology of the patients.

Microorganism*	Tracheal secretion (+) No.(%)	Blood (+) No.(%)	Nasal smear (+) No.(%)	Urine (+) No.(%)
Streptococcus pneumonia	2 (8.3)	5 (20.8)		
MSSA	8 (33.3)	6 (25)		
MRSA	3 (12.5)	1 (4.1)		
Pseudomonas aeruginosa	13 (54.1)	5 (20.8)	6 (25)	
Klebsiella pneumonia	8 (33.3)			4 (16.6)

*In some cultures more than one organism was isolated from same and/or different specimens. MSSA: Methicillin sensitive Staphylococcus Aureus, MRSA: Methicillin resistant Staphylococcus Aureus.

tion (Table 1). CRP and PCT levels also were significantly higher in Group 1 patients than other patients (Figure 1, 2). After antimicrobial treatment, CRP and procalcitonin levels were decreased in both Group 1 and Group 2. But in Group 2, difference in PCT levels was not statistically significant (Figure 3, 4). CPIS and CURB-65 scores were decreased in all patients median 8 days after ICU admittance.

DISCUSSION

C-reactive protein and procalcitonin are used as parameters to support the diagnosis of infection.[17,18] It has been written that CRP levels were highest in bacterial infection.[19] Therefore, some of the patients show normal levels of CRP during COPD exacerbations because of lack of infection, and exacerbations might be caused by viruses or concomitant heart failure requiring different treatment. In agreement to this report, CRP levels were higher in pathogen isolation achieved cases than patients without pathogen isolation in our study. In a study, it was demonstrated that antibiotic administration within 4 h of hospital admission resulted in a marked increase in misdiagnosis and inappropriate antibiotic utilization.[20] Similarly in our practice, most of the patients with COPD exacerbation were started empiric antibotherapy immediately after ICU admittance. We hypothesized that if we measure inflammatory markers before the begining of antibiotic treatment it might be helpful for the decision of initiation of this therapy. Briel et al reported that PCT guidance in antibiotic usage avoided unnecessary antibiotic use.[21] In our results both CRP and PCT levels were found high which was comparable with the microbiologic culture results. Also we combined assessment of CPIS and CURB-65 scores in order to support the accuracy of infection. In a study combination of PCT and CPIS score worked to exclude misdiagnosis of ventilator associated pneumonia.[22] Another recent study showed procalcitonin might aid in identifying Pneumonia Severity Index/CURB 65 high-risk patients.[23] We determined that patients with bacterial infection showed high severity scores. Nevertheless, it was suggested in a review that antibiotic therapy significantly decreased mortality and lack

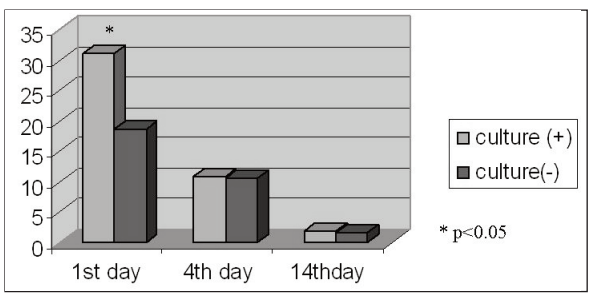

FIGURE 1: CRP levels according to microbiological examination.
culture (+): Group 1, culture (-): Group 2-3.

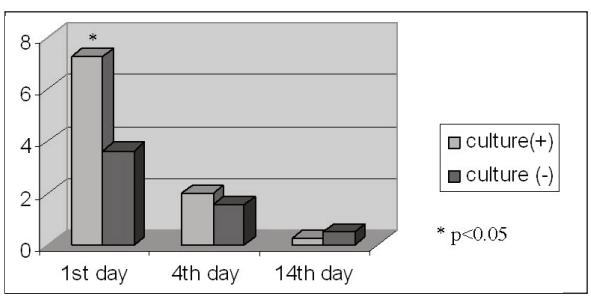

FIGURE 2: PCT levels according to microbiological examination.
culture (+): Group 1, culture (-): Group 2-3.

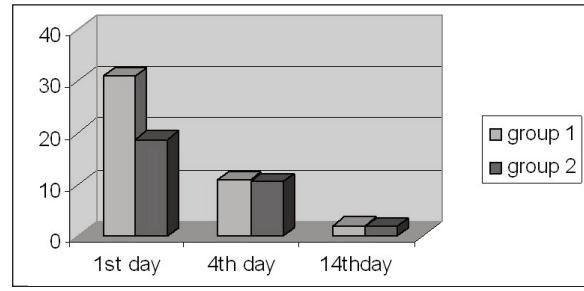

FIGURE 3: CRP levels according to antibiotic treatment.

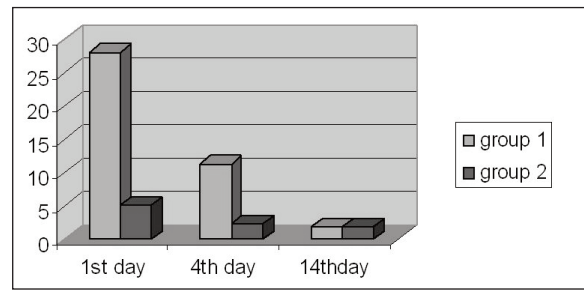

FIGURE 4: PCT levels according to antibiotic treatment.

of response to treatment in patients with COPD exacerbation.[24] Eleven trials with 917 patients were included in this review. Ten trials had used diagnostic criteria of increased cough, sputum volume and purulence for COPD exacerbation as indicators of bacterial infection. In this review antimicrobial therapy was supported according to the results of decrease in mortality.

Adequate antibiotic treatment, which means coverage of all pathogens isolated, and determined by the sensitivity pattern in the antibiogram, should definitely be considered in infected COPD cases. According to our results, management of patients with negative microbiologic examination might need the aid of inflammatory marker levels in order to give correct decision.

As a conclusion, appropriate antibiotherapy is essential in the patients admitted to ICU with COPD exacerbation. Initiation of antimicrobial therapy may be manipulated by the levels of CRP and procalcitonin. This study gives a minor but encouraging result. Further studies with larger number of cases are necessary to confirm the data and to establish the use of these data in practice.

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