The Comparison of Procalcitonin Guidance Administer Antibiotics with Empiric Antibiotic Therapy in Critically Ill Patients Admitted in Intensive Care Unit

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Abstract- The empiric antibiotic therapy can result in antibiotic overuse, development of bacterial resistance and increasing costs in critically ill patients. The aim of the present study was to evaluate the effect of procalcitonin (PCT) guide treatment on antibiotic use and clinical outcomes of patients admitted to intensive care unit (ICU) with systemic inflammatory response syndrome (SIRS). A total of 60 patients were enrolled in this study and randomly divided into two groups, cases that underwent antibiotic treatment based on serum level of PCT as PCT group (n=30) and patients who undergoing antibiotic empiric therapy as control group (n=30). Our primary endpoint was the use of antibiotic treatment. Additional endpoints were changed in clinical status and early mortality. Antibiotics use was lower in PCT group compared to control group (*P*=0.03). Current data showed that difference in SOFA score from the first day to the second day after admitting patients in ICU did not significantly differ (*P*=0.88). Patients in PCT group had a significantly shorter median ICU stay, four days versus six days (*P*=0.01). However, hospital stay was not statistically significant different between two groups, 20 days versus 22 days (*P*=0.23). Early mortality was similar between two groups. PCT guidance administers antibiotics reduce antibiotics exposure and length of ICU stay, and we found no differences in clinical outcomes and early mortality rates between the two studied groups.

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Keywords: Procalcitonin; Antibiotics; Intensive care unit; Systemic inflammation syndrome

Introduction

The critically ill patients with sepsis usually undergo antibiotic empirical treatment (1). This strategy results in antibiotic overuse and increase in the cost and bacterial resistance (2). These patients initially present with systemic inflammatory response syndrome (SIRS). SIRS is seen after trauma, major operation, severe inflammation and infections (3).

Patients with SIRS undergo supportive therapy except SIRS due to an infection that is diagnosed as sepsis and needs early administration of antibiotic and control of infection (4). The prognosis of sepsis is worse than SIRS and differentiation between them is vital for the intensivist. Outcomes of critically ill patients with sepsis can improve if these patients receive prompt and appropriate antibiotic therapy (5). The diagnosis of sepsis in critically ill patients is probably delayed because sign and symptoms of infection can be missing due to alteration in immune status as well as the exposure to specific treatment and procedures. In addition, because of the low specificity of diagnosis of sepsis in critically ill patients and fear of not treating life-threatening infection, leads intensivist to overuse of antibiotics in ICU (6).

These issues lead to the development of new biomarkers that accurately predict sepsis in these patients. Previous studies have showed that serum level of procalcitonin (PCT) increased in patients with sepsis, and this marker is accurate in the diagnosis of sepsis (7,8). Normal serum levels of PCT are below 0.5 ng/mL and patients with serum levels above 2 ng/mL are more likely to develop sepsis (9). Serum half time of PCT is 24-36 hours. After injection of Ecoli

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endotoxin to healthy volunteer, we can detect PCT in serum after four hours and then increase till reach to plateau phase during 8- 24 hours. One meta-analysis of 33 studies showed that PCT in is superior to C-reactive protein (CRP) for differentiating SIRS and sepsis (8). Meynaar reported that PCT is more useful for differentiation of sepsis and SIRS than CRP, interleukin-6 (IL-6) and lipopolysaccharide-binding protein (LBP) with positive predictive value of 88% and negative predictive value of 97%. They concluded PCT is the best marker for discrimination between sepsis and SIRS in critically ill patients (10).

It was shown that PCT is a useful guide for initiation of antibiotic in patients with respiratory infection (11). Moreover, PCT-guided treatment can decrease the duration of antibiotic therapy in critically ill patients (12). Also, one study concluded that PCT guide treatment in patients with lower tract respiratory infection decreased antibiotic consumption up to 46.4% and clinical outcomes, and mortality were similar to patients who underwent empirical antibiotic treatment (13). The aim of the present study was to evaluate the effect of PCT guide treatment on antibiotic use, clinical outcomes and early mortality of critically ill patients admitted to ICU.

Materials and Methods

This single center prospective, the single-blind randomized study was performed from December 2012 to December 2013 in the 30 bed mixed ICU in our hospital. Sixty of 140 screened patients for eligibility were randomized into two groups, 30 cases in PCT and 30 cases in the control group. This study was approved by the ethical committee of our hospital. Written informed consent was obtained from all patients. Patients with at least two of the four criteria including body temperature above 380C or below 360C, tachycardia >90/min, tachypnea >20/min and leucocytosis >12×109/L or a leftward shift with more than 10% band cells or leucopenia <4×109/L were defined as subject with SIRS and recruited in this study (3).

The reasons for exclusion were as followed: documented infection, pus from wound or abscess, empyema, thrombophlebitis, infection due to viral or parasites, hypoxemia (PO2<60 mmHg), oliguria (urine output <30 ml/hr), Glasgow coma scale (GCS) 3 without sedation, parenteral antibiotic usage 24 hours before admission to ICU, hospitalization 48 hours before enrollment, conditions requiring prolonged antibiotic therapy such as endocarditis, chronic localized infection such as osteomyelitis and severely immunocompromised patients. All participants were randomly divided into two groups by computer based random number generation, cases that with antibiotic treatment based on serum level of PCT as PCT group and patients who received antibiotic empiric therapy as a control group. Sepsis workup including blood culture, urine culture, bronchoalveolar lavage fluid and tracheal aspirates culture was performed for all cases after admission.

In this study when microbiological cultures were available, broad-spectrum parenteral antibiotics were administered based on results of cultures. PCT levels were measured during 4-6 hours by using a time-resolved amplified cryptate emission (TRACE) assay (Kryptor Compact; Brahms, Germany). In case group, according to serum level of PCT, patients were divided into three groups as: PCT level 0.5 ng/ml or less (group A), PCT value of 0.5-2 ng/ml (group B) and PCT level 2 ng/ml or more (group C) (14). Group A indicated a low probability of bacterial infection and use of antibiotics was discouraged, and PCT level rechecked after 12 hours. In group B with a medium probability of infection antibiotic therapy was not administered and PCT level rechecked after eight hours.

In group C with a high probability of bacterial infection patients underwent antibiotic treatment. If the level of PCT was higher than 2 ng/ml after recheck in group A and B, antibiotics therapy was administered and if level of PCT was lower than 2 ng/ml, patients underwent close observation and PCT rechecked until culture results were obtained. Our primary endpoint was the use of antibiotic treatment. Additional endpoints were changed in clinical status and early mortality. Clinical status was evaluated by sequential organ failure assessment score (SOFA) and minimized the effects of patients' primary condition at the time of admission by matching them with acute physiology and chronic health evaluation score (APACHE II). We designed our trial to enroll 60 patients, and this number gave the study 95% power to detect a 30% reduction in the use of antibacterial agents.

Discrete variables expressed as counts (%) and continuous variables were mentioned as mean ± SD. Quantitative data were compared with t-test, a 5% level of significance. We analyzed comparability of PCT group and control group by $\chi 2$ test. The effects of intervention and confounding factors in both groups were controlled by a statistical model of repeated measurement by general linear model.

Results

The mean of the age in PCT group was 40.2 ± 17.7 years and in the control group was 40.7 ± 20.9 years (*P*=0.92). Ten cases (33.3%) in PCT group and 12 cases (40%) in the control group were female (*P*=0.11). Baseline characteristics of both groups are shown in Table 1. The demographic and preoperative characteristics were similar in both groups. The mean APACHE score in PCT group was 11.9 ± 9.3 and 13.3 ± 7.9 in a control group that was not significantly meaningful (*P*=0.54). Based on PCT level in case group 6 patients (20%) were in group A, 13 patients (43.3%) in group B and 11 patients (36.6%) were in group C.

Table 1. Baseline characteristics of two groups

Characteristic	PCT group (n=30)	Control group (n=30)	*P*. value
Age, yr, mean ± SD	40.2±17.7	40.7±20.9	0.92
Female sex, n (%)	10 (33.3%)	12 (40%)	0.11
Respiratory failure, n (%)	18 (60%)	16 (53.3%)	0.62
Heart failure, n (%)	3 (10%)	2 (6.6%)	0.70
Renal failure, n (%)	6 (20%)	8 (26.6%)	0.48
Diabetes mellitus, n (%)	6 (20%)	5 (16.6%)	0.51
COPD, n (%)	5 (16.6%)	6 (20%)	0.96
ARDS, n (%)	6 (20%)	8 (26.6%)	0.58
Shock, n (%)	12 (40%)	14 (46.6%)	0.74
Acidosis, n (%)	14 (46.6%)	13 (43.3%)	0.62
Dialysis, n (%)	2 (6.6%)	3 (10%)	0.80
Ventilator support, n (%)	12 (40%)	10 (33.3%)	0.52
Vasopressor needed, n (%)	10 (33.3%)	11 (36.6%)	0.38
APACHE II score, mean ± SD	11.9±9.3	13.3±7.9	0.54
SOFA score, n (%)	5.4±3.6	5.7±2.8	0.84

One case of group B after recheck of PCT had PCT level more than 2 ng/ml, and antimicrobial agents were administered for him. Blood cultures were positive in 10 patients (33.3%) of the PCT group and 11 patients (36.6%) of the control group. Among patients with negative blood culture 2 patients had PCT>2 ng/ml, 8 patients had PCT 0.5 -2 ng/ml and 10 patients had PCT<0.5 ng/ml. In patients whose blood culture was negative, the antibiotic was discontinued. The causative microorganism did not differ significantly between the PCT and control group.

The most frequent microorganism in both groups was staphylococcus aureus, *Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Klebsiella*, *Streptococcus pneumonia* and Escherichia *coli*. The dose and type of antibiotics were same in both groups. Antibiotics exposure was lower in PCT group compared with control group. Total antibiotic exposure days were lower in patients from the PCT group compared with control group (128 vs. 320 days respectively, *P*=0.003). The clinical cure after antibiotic therapy resulted in 27 patients (90%) of PCT group compared 26 patients (86.6%) in the control group (*P*=0.38). Average SOFA score in PCT group on the first day after admission was 5.4±3.7 and in the second day was 5.4 ± 4.2 and in control group was 5.7 ± 2.8 and 5.7 ± 3.8, respectively (*P*=0.88). Limiting the effect of APACHE II score in analytic model showed that difference in SOFA score from the first day to the second day after admitting patients in ICU did not significantly differ (*P*= 0.29) and one can conclude that therapeutic method had not any effect on SOFA score in both groups. Also, in comparison of SOFA score of first and second day between patients with PCT level below 2 ng/ml and control group we identify that this variable was not significantly different (4.40 ± 3.01 and 4.12 ± 3.05 versus 4.35 ± 1.61 and 3.82 ± 2.37, *P*=0.62). Patients in PCT group had a significantly shorter median ICU stay compared to control group, 4 days; range 2-20 days, versus 6 days; range 2-28 days, respectively (*P*=0.01).

Hospital length of stay was not statistically significant different between the two groups, 20 days; range 8-44 days in PCT group, versus 22 days; range 6-65 days in the control group, respectively (*P*=0.23). Hospital mortality was similar between two groups, 5 patients (16.6%) in PCT group versus 4 patients (13.3%) in the control group (*P*=0.71). The comparisons of outcomes in both groups are shown in Table 2.

Table 2. The comparison of outcomes in both groups

Variables	PCT group (n=30)	Control group (n=30)	*P*. value
Total antibiotic exposure days	128	320	0.003
SOFA score in the first day, mean ± SD	5.4±3.6	5.7±2.8	0.76
SOFA score in the second day, mean ± SD	5.4±4.2	5.76±3.8	0.88
Clinical cure, n (%)	27 (90%)	26 (86.6%)	0.38
In-hospital mortality, n (%)	5 (16.6%)	4 (13.3%)	0.71
ICU stay, median day (range)	4 (2-20)	6 (2-28)	0.01
Hospital length of stay, median day (range)	20 (8-44)	22 (6-65)	0.23

Discussion

We observed a significant reduction in antibiotics use without significant changes in clinical outcomes, ICU stay and hospital mortality in present study based on the use of algorithm that administered antibacterial agents by check of PCT level in patients with SIRS admitted in ICU. This method was safe and did not compromise clinical outcomes. Based on current data level of PCT less than 2 ng/ml can indicate patients without clinically bacterial infection and these subjects do not need antimicrobial therapy. The duration of antibiotic therapy in critically ill patients in ICU is usually based on empirical rules. This strategy resulting in antibiotic overuse, development of bacterial resistance, and increasing costs (15,16). Significant progress has been made to reduce the duration of antibacterial therapy in patients in the last years. Much endeavor has been put into find a specific and sensitive biomarker to guide intensivist for antibiotic therapy in critically ill patients (17). To attain this goal, the user preference parameter would be noninvasive and readily available for clinicians. Many studies have showed that PCT is more accurate than other routine biomarkers for diagnosis of bacterial infection (18-25). Meynaar in his single center prospective study identified that serum PCT is more valuable than CRP, IL-6, and LBP in the differential diagnosis of SIRS from sepsis in patients in ICU (10).

Trial of Charles suggested that in critically ill patients admitted to ICU, any increase in PCT, in addition to clinical finding should warn the intensivist toward the risk of bacterial infection after excluding other causes of rising of PCT such as trauma, recent operation and cardiac arrest (26). In many centers, a minimum of duration for empiric of parenteral antibiotic therapy is 14 days in the context of sepsis. In present study PCT, guidance treatment reduced the duration of antibiotic therapy in critically ill patients with SIRS admitted to the ICU. This finding was consistent with Nobre trial that indicated total antibiotic exposure days is 504 days in PCT group compared to 655 days in control group respectively (*P*=0.07) (27). Present results supported findings from previous studies that showed PCT guidance antibiotic treatment decreases antibiotic exposures in critically ill patients with sepsis and that this algorithm is not associated with worse outcomes (10,20,28). Reducing antibiotic use has many benefits in critically ill patients. By limiting the exposure to antibiotics, we can potentially avoid resistance to antibiotics and reduce t risk of cross-contamination with these resistant microorganisms (29). Moreover, increase in duration of antibacterial therapy is associated with costs, especially when broad-spectrum agents are administered (2). In addition, costs decrease due to the reduction of hospital and ICU length of stay leading to a shorter duration of parenteral antibacterial treatment (20). It was shown that a delay of more than eight hours in the administration of antimicrobial therapy is associated with increased mortality (30).

Thus, the important question that may be asked is: do we have permission to postpone antibiotic therapy in patients admitted with suspected SIRS, if his PCT to be less 2 ng/ml? The answer depends on our initial estimation of the clinical condition of patients and pretest probability. Moreover, we know that PCT is the most accruable biomarker that is known in discrimination of SIRS from sepsis in critically ill patients. Meynaar found that if PCT level is below 2 ng/ml in the first 24 hours after admission, bacterial infection is unlikely and showed the negative predictive value of PCT was 97% (10). Also he identified that in PCT level more than 10 ng/ml, sepsis was very likely with positive predictive value of 88% (10).

These results show that PCT is more reliable than other biomarkers that are identified to differentiate sepsis from SIRS in critically ill patients. On the other hand during the period that we postponed administration of antibiotic therapy, patients were under close observation, and if we suspected sign and symptoms of bacterial infection, we administered antibiotic therapy promptly. In present study neither a deterioration of

clinical condition in our patients based on SOFA nor increased hospital mortality was noted in PCT group. Current results were consistent with other studies that reported PCT guidance treatment substantially was safe and did not compromise clinical outcome and without increase mortality (20,21). We reviewed the literature and found that the majority of previous studies have evaluated the safety and efficacy of PCT guidance antibiotics treatment for with-holding antimicrobial agents but the study that evaluated the administration of antibiotic based on PCT level similar our study was rare. Several limitations of our study should be mentioned. First, this study is a single center with a small sample size of cases. Although we did not identify deterioration in clinical outcome and did not find signal of higher mortality, we could not completely exclude a potential damage of postponing start of antibacterial treatment in critically ill patients admitted with SIRS in ICU based on PCT guidance. Second, because this study was a single-blind study design, the intensivist was aware of the group of patients creating a certain amount of bias. Finally, we could not extend the algorithm of this study to all patients admitted to the ICU with a diagnosis of sepsis or SIRS.

We excluded infections that needed prolonged treatment and difficult to treat bacterial infection and also severely immunocompromised patients. We must consider that although PCT is the best marker to segregation of SIRS from sepsis, but we should not justify the clinical decision based on PCT alone. Distinguishing SIRS from sepsis still requires association of clinical parameters (10). The limitation of our study was the small sample size, and we recommend designing another study with more patients. In conclusion, our strategies based on PCT guidance administer antibiotics in patients with SIRS hospitalized in ICU reduce antibiotics exposure and length of ICU stay. We found no differences in clinical outcome and hospital mortality rates among patients treated based on PCT guide and patients underwent routine empirical treatment. We recommend a multicenter trial with a large number of patients with SIRS to evaluate the safety and efficacy of PCT guidance protocol and its effect on antibiotic exposure, ICU and hospital stay, clinical outcome and mortality.

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