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Full Length Research Paper

Procalcitonin and white blood cell count (WBC), erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) alterations in children with systemic inflammatory response syndrome before and after treatment

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Systemic inflammatory response syndrome (SIRS) due to infection is an important cause of morbidity and mortality in children. The present prospective observational study aimed to determine the correlation between procalcitonin (PCT) and white blood cell count (WBC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in toddlers before and after treatment. Moreover, 50 patients aged 1 to 36 months who were hospitalized at the Pediatrics Ward in Besat Hospital, Sanansaj city, Kurdistan province Western Iran through a census sampling method were recruited. The complete blood count (CBC) was measured via cell counter; ESR by the Westergren method, CRP via semi quantitative method and PCT via semi quantitative immune-chromatography method. Pearson correlation coefficient was used to estimate correlation between WBC, ESR, CRP and PCT before and after treatment of SIRS. The results obtained show correlation coefficients between PCT and CRP as well as between PCT and ESR in the first day of trial before treatment were determined as 'good' and 'moderate', respectively. However, there was no significant correlation between PCT and WBC. No significant correlation was found between PCT and WBC count, ESR and CRP at the third day of treatment. It was concluded that procalcitonin and CRP is the most favorable values for confirming SIRS diagnosis in the onset of treatment. PCT can be considered as the marker of choice for following up purposes.

Key words: Systemic inflammatory response syndrome (SIRS), procalcitonin, toddlers, treatment.

INTRODUCTION

The systemic inflammatory response syndrome (SIRS) is a clinical expression of inflammation and can be initiated by a variety of infectious or non-infectious causes (Whang et al., 1998). SIRS can be self-limiting or may progress to severe sepsis or septic shocks (Mokart et al., 2005) and its criteria such as fever, tachycardia and tachypnoea are fairly non-specific features of various

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underlying diseases (Hochreiter et al., 2009). Traditional markers such as body temperature, heart rate, respiratory rate or white blood cell (WBC) count, might be unspecific (Rey et al., 2007). Besides these clinical signs and symptoms, other markers are also required warning the physicians about risks of current systemic inflammation (Charles et al., 2008). In practice, physician estimate the chance that a patient will become infected on clinical grounds and on rapid tests, such as white blood cell count, C-reactive protein (CRP) and procalcitonin. The blood concentrations increase rapidly after the onset of an inflammation (Lacroix, 2007).

Procalcitonin (PCT), a polypeptide consisting of 116 amino acids, is the precursor of calcitonin (Sponholz et al., 2006) and occurs in very low concentrations in the serum of healthy people (Ballot et al., 2004). Procalcitonin is almost undetectable under physiological conditions. The normal ranges of procalcitonin in blood are lower than 0.1 ng/ml with a cut-off point of 1 or 2 ng/ml (Lacroix, 2007; Hatherill et al., 1999). C-reactive protein and procalcitonin are two acute-phase reaction proteins of the inflammatory process (Lacroix, 2007). Recently, a semi-quantitative PCT test kit has become commercially available. This kit is easy to use at the bedside, providing rapid results and requiring a very small amount of blood (Boo et al., 2008).

Some studies have provided conflicting results on the diagnostic accuracy of PCT in critically ill patients and have highlighted the importance of integrating laboratory and clinical evaluations (Tsangaris et al., 2009). Even though, some studies have underscored its value in a variety of clinical conditions for identifying infectious processes, characterizing the severity of the underlying illness, guiding therapy and risk stratification (Sponholz et al., 2006). There is also a conflicting result regarding the prognosis value of PCT (Charles et al., 2009). The diagnostic and prognostic accuracy of routine PCT measurements is also disputable (Harbarth et al., 2001). Despite several reports regarding treatment process in patients with systemic infection, only few are available about children with SIRS (Müller and Becker, 2001). Conflicting results about the role of PCT, indicates necessary needs to define its utility for SIRS appropriately. In the present prospective observational study, the leukocyte count, CRP, erythrocyte sedimentation rate (ESR) and PCT plasma concentrations were measured in children admitted to the hospital when it was considered clinically necessary. The study therefore was aimed to evaluate the measurement of PCT in children one to three years old, to be compared with C reactive protein and the leukocyte count and ESR before and after treatment of SIRS.

MATERIALS AND METHODS

This was a prospective observational study carried out between July 2008 and July 2009, enrolling children aged 1 to 36 months, admitted to the Pediatric Ward, Beasat Hospital Sanandaj city western Iran and diagnosed with SIRS. Children were excluded from the study, if they had chronic systemic inflammatory diseases, degenerative neurological and immunodeficiency diseases. Meanwhile children under corticoid therapy, non-steroidal anti-inflammatory or antibiotics drugs for more than 24 h, those who suffered from traumas or burns or those who were in postoperative care units were excluded from the study. Diagnosis of SIRS was defined according to the guidance established by the Consensus Conference of 2001, the American College of Chest Physicians, the Society of Critical Care Medicine Consensus Conference (Hochreiter et al., 2009; Castelli et al., 2004). The diagnosis was based on presence of two or more criteria including a) auxiliary temperature of ≥37.7°C in infants one to three months and > 38.5°C or < 36°C in children between three months to three years; b) tachycardia (may be absent in hypothermia); PR>120 in infants < 1 year and PR>110 in one to three years old children; c) tachypnea; RR>40 in infants < 1 year and RR>30 in one to three years old children and d) white blood cell count high or low for age (and not secondary to chemotherapy); >15000 or <5000 in infants < one year and < 6000 in one to three years old children. In addition, at least one of the clinical symptoms including altered state of consciousness, hypoxemia, increased serum lactate or wide pulses had to be present.

Laboratory tests

After getting a written consent from parents, children blood specimens were obtained investigating leukocyte count (WBC), procalcitonin (PCT), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). WBC counts were measured by Sysmex KX21; PCT by semi quantitative immune-chromatography method (BRAHMS, PCT, Q kit), CRP by semi quantitative method (CRP Blue Spot, Applied Research and Technology in Biosciences, BIO A.R.T.), and ESR by Westergren method. Chest radiography, cerebrospinal fluid culture, tracheal aspirate culture and urine culture were also done whenever clinically indicated. Antibiotics were commenced after the blood specimens were collected. The decision to stop antibiotics was based on clinical features. Before starting the treatment process, the first blood sample was taken on admission followed by a sample taken 72 h after treatment. Specimens of blood (of at least 0.5 ml) were obtained from each infant by a sterile technique and were inoculated into commercially-prepared devices at the bedside (BD Bactec Peds Aerobic/F vials; Becton Dickenson, Shannon Country Clare, Ireland). The inoculated vials were transferred to the microbiological laboratory and inserted into a BACTECT Fluorescent series instrument for incubation and periodic reading (BACTECT 9240, Becton Dickenson, Shannon Country Clare, Ireland). Leukocyte count (WBC), ESR, PCT and CRP were measured within the first 12 h of admission when considered necessary by the physician in charge for the patient clinical care. Blood samples were drawn into green-top tubes, containing lithium-heparin as anticoagulant, for determination of CRP and PCT.

Statistical analysis

The chi-square test (or Fisher's test for expected value of < 5) was used for analysis of categorical variables. The independent sample *t*-test was used for analysis of continuous variables with a normal distribution and to compare differences between CBC, ESR, CRP and PCT before and after treatment of SIRS. Mann-Whitney U-test was used for those with a skewed distribution. P values of < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 17. The study was approved by the

Table 1. Comparison the results of PCT and CBC, ESR, CRP before and after treatment.

Blood component	Factor	First day, n (%)	Third day, n (%)	*P* value
WBC	Normal	7 (14)	64 (32)	0.02
	Abnormal	86 (43)	36 (18)	
ESR	Normal	74 (37)	88 (44)	0.05
	Abnormal	26 (13)	12 (6)	
CRP	Normal	42 (21)	80 (40)	0.04
	Abnormal	58 (29)	20 (10)	
Procalcitonin	Normal	34 (17)	100 (100)	<0.001
	Abnormal	66 (33)	0 (0)	

Table 2 Correlation coefficient between PCT and CBC, ESR, CRP before and after treatment.

PCT	First day, R	*P value*	Third day, R	*P value*
WBC	0.11	0.4	0.08	0.5
ESR	0.29	0.04	0.04	0.8
CRP	0.65	0.01	0.07	0.6

Ethics and Research Committee at the Kurdistan University of Medical Sciences.

RESULTS AND DISCUSSION

The mean age ± standard deviation of children was 17.01 ± 10.14 months. Overall, 58% of children (n = 29) were male and 42% (n = 21) were female. About one third of the first day procalcitonin before treatment (34%, n = 17) was normal. WBC count, ESR and CRP measurements were abnormal in 43, 13 and 28 children respectively. PCT in all patients was returned to the normal values in the third day after treatment. However, WBC in ten patients, ESR in six patients and CRP in ten patients remained abnormal (Table 1). Correlation coefficients between PCT and CRP as well as between PCT and ESR in the first day of trial before treatment were determined as ‘good’ and ‘moderate’, respectively. However, there was no significant correlation between PCT and WBC. No significant correlation was found between PCT and WBC count, and ESR and CRP at the third day of treatment (Table 2).

In the present study, the correlation of plasma levels of PCT with CRP, ESR and WBC in patients with SIRS, were measured and compared before and after treatment. Regarding the primary outcome, PCT performance was better than other widely used infection markers, such as CRP and ESR and WBC count. Despite being considered as a surrogate sign of systemic inflammation, SIRS criteria are not always the result of a systemic infection. Standard laboratory variables such as CRP have a slow kinetic profile; the same applies for the leukocyte count predicted. It has convincingly shown that PCT values could differentiate SIRS from sepsis patients. It was demonstrated that PCT value was rapidly decreased to the reference values in successfully treated patients, whereas SIRS patients in the absence of infection, revealed PCT values less than 1 ng/ml throughout the clinical course (Castelli et al., 2004). Assuming that PCT secretion is induced by cytokines release, it is closely related to the inflammatory process, thus high PCT levels are expected in the course of non-infectious illnesses associated with marked inflammatory response.

A cut-off point of 1.1 ng/ml could distinguish patients with SIRS from those with sepsis in the ICU (Schroeder et al., 2009). In the third day after treatment, all patients had a normal PCT indicating that PCT performs better than other widely used infection markers, such as ESR, CRP and WBC count in the onset of SIRS treatment. These data confirms that PCT concentrations modulate more quickly than CRP. In the present study, PCT proved to be more specific than CRP. These data might indicate that PCT, but not the other mentioned markers, could be used to test children' response to antibiotics. The surprising finding was negative blood culture for all 50 patients. The lack of positive culture results cannot exclude infection, and the traditional definition of SIRS has limited value, because many patients might had SIRS criteria due to their status, whereas clinical evaluation remains sometimes the only rational approach

(Tsangaris et al., 2009). Although this is mainly based on clinical course and symptoms, biochemical inflammation and sepsis markers are often indispensable to establish the diagnosis (Castelli et al., 2004). Recent studies upgraded that a patient with a low PCT, does not have bacterial sepsis (Tsangaris et al., 2009). Recently, the International Pediatric Sepsis Consensus Conference modified the adult systemic inflammatory response syndrome (SIRS) criteria for children (Suprin et al., 2000).

PCT permitted earlier diagnosis of infection or inflammation since the plasma PCT concentration increased sooner. Besides, PCT returns to the normal range more rapidly than CRP (Schroeder et al., 2009). After 6 h from starting SIRS, PCT was elevated and its elevation was faster than CRP, therefore PCT can be considered as a better marker. This is consistent with previous findings (Rey et al., 2007). On the other hand, any alteration in PCT values was correlated with the systemic inflammatory response. All parameters have different kinetics and profiles of induction. Faster kinetics of PCT was compared to the other markers, making it a better parameter for severity estimation, prognosis and time course of disease (López Sastre et al., 2006).

Procalcitonin is relatively a new diagnostic biomarker used in promoting the SIRS for hospitalized children. Clinically, PCT is an important serum marker for systemic inflammation in which elevated serum PCT reflects the clinical course (Whang et al., 1998). In our experience, PCT was sensitive enough to be included in a staging system for SIRS in pediatric patients. These findings are consistent with other studies in which CRP and especially PCT, may become a helpful clinical tool for stratifying children with SIRS, and therefore should be included in clinical practice in intensive units (Rey et al., 2007; Becker et al., 2004). In severe inflammation, serum levels of PCT are noticeably elevated and levels of serum PCT correlate with the severity of the illness positively. The main finding of the present study was that PCT monitoring retains its diagnostic value for a similar population presenting solely with a new episode of SIRS and fever without confirmed infection. However, there is conflicting finding in which CRP was more reliable than PCT for distinguishing septic patients and SIRS children without infection (Suprin et al., 2000).

A recent systematic review showed that the diagnostic accuracy of PCT was greater than that of CRP for distinguishing between bacterial infection and SIRS among hospitalized patients. PCT but not CRP is also able to differentiate between SIRS and sepsis. In the present study, an elevated serum PCT level (>0.5 µg/L), with the highest value of 5.34 µg/L, was observed in almost half of non-infectious SIRS patients (48%), implying the possible role of other sepsis to increase the synthesis and release of PCT (Arkader et al., 2006). The main limitation of the present study was the lack of a good standard to calibrate the diagnostic criteria. The children modified version of SIRS/sepsis definitions was used in the present study which might be controversial. Moreover, any generalization of the provided findings in the present study should be cautious due to moderately small sample size. In the onset of treatment and for confirming the diagnosis of SIRS, procalcitonin and CRP are the most favorable values for confirming SIRS diagnosis in the onset of treatment. PCT can be considered as the marker of choice for follow up purposes.

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