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Procalcitonin Levels Compared With CRP and ESR Levels in Septicemic Children Aged 3 Months to 13 Years in the Pediatric and PICU Wards of Ayatollah Mousavi Hospital, Zanjan

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Abstract

Background: Procalcitonin (PCT) levels are increased in sepsis. In most previously conducted research, PCT levels were found to increase during septic shock.
Objectives: The purpose of this study was to compare PCT levels with CRP and ESR levels in children with systemic inflammatory response syndrome (SIRS), sepsis, and septic shock.
Methods: This cross-sectional study was conducted between December 2011 and December 2012 on 84 children between 3 months and 13 years old admitted in pediatric and PICU wards. The required venous samplings were taken during their hospitalization prior to antibiotic therapy. Urine and CSF fluid cultures were analyzed in specific cases. Patients treated with intravenous antibiotics during the week prior to admission were not included in the study.
Results: Due to incomplete information, a total of 81 children were examined; of them, 31 were suffering from SIRS (36.9%), 27 had sepsis (32.1%), 10 had undergone septic shock (11.9%), and 13 had positive cultures (15.5%). PCT levels were higher than 0.5 ng/mL in 57.1% of the patients, CRP levels were higher than 10 mg/L in 71.4% of the patients, and ESR levels were higher than 20 mm/h in 69% of the patients. In our study, a moderate correlation was found between PCT and CRP levels. However, there was a poor correlation between PCT and ESR levels.
Conclusions: PCT levels are a faster and more reliable marker of inflammation than ESR or CRP levels. However, since PCT tests are expensive, CRP levels are preferable to study in differentiating the three stages of infection.

Keywords: Procalcitonin, Sepsis, Septic Shock, Systemic Inflammatory Response Syndrome, CRP, ESR

1. Background

Sepsis is a serious disease that can be life threatening. Its symptoms are highly variable and dependent on the patient's age, the underlying disease, and the type of organism (1). Several biomarkers have been suggested for the early diagnosis of sepsis, including IL-1b, IL-8, TNF-α, and PCT (2, 3). Located in the lower range in normal subjects, PCT, a calcitonin prohormone, increases significantly in patients with bacterial infections caused by a broad spectrum of gram-positive and gram-negative bacteria (2). In three separate studies, the sensitivity of PCT in the diagnosis of sepsis was found to be 97%, 78%, and 85%, while WBC, CRP, and ESR levels did not have high accuracy in the diagnosis of bacterial infection in immunocompromised and neutropenic patients (4-6). Therefore, PCT could be used as a valuable marker for differentiating SIRS from sepsis (7). The level of PCT in plasma is less than 0.5 ng/mL in healthy people, 0.5 - 2 ng/mL in patients that may have sepsis, 2 - 10 ng/mL in patients with sepsis, and higher than 10 ng/mL in patients experiencing septic shock (8). In the case of suspected sepsis, drug therapy is performed immediately after the patient's admission to hospital, as any delay in treatment can worsen the disease (1). However, delays can occur due to the lack of specific symptoms of sepsis or inaccurate microbial culture results. Blood cultures may be negative for various reasons, such as the use of antibiotics before hospital admission, which is common in our society, although the results of blood cultures are reported after at least 48 hours. They may also be negative in the early stages of SIRS and sepsis. Moreover, many organisms require specific media and exclusive culture environments that are not available in most medical centers. However, microbial cultures do not reflect the host's inflammatory responses nor do they detect organ dysfunction (2, 3).

Therefore, by measuring serum PCT, antibiotic therapy can be commenced or terminated to help doctors with the diagnosis of suspected sepsis (9). Compared with CRP and ESR levels, PCT levels are a better marker in diagnosing lobar pneumonia in children (10).

2. Objectives

Because measuring CRP and ESR levels is more cost effective than measuring PCT levels in the diagnosis of SIRS, sepsis, and septic shock as well as their differentiation from one another, we decided that, in addition to determining the quantitative amounts of CRP, ESR, and PCT, their Kappa coefficients and their correlations should also be determined.

3. Methods

This cross-sectional study was conducted on children aged between 3 months and 13 years admitted to the pediatric and PICU wards of Ayatollah Mousavi hospital in Zanjan between August 2011 and August 2012. In total, 84 children consisting of 43 males (51.2%) and 41 females (48.8%) were analyzed in four groups: those diagnosed with suspected infection, those with SIRS, those with sepsis, and those who underwent septic shock. Children treated with intramuscular or intravenous antibiotics during the week before their hospitalization were not enrolled in the study. Written informed consent was obtained from all the patients and their guardians, and all the patients were examined clinically. Patients' characteristics, including their ages; sexes; rectal temperatures; respiratory rates; heart rates per minute; systolic and diastolic blood pressures; alertness statuses at the time of admission and during hospitalization; underlying diseases, such as congenital disease; requiring resuscitation at the times of admission and during hospitalization; and the need for vasopressors or drugs during hospitalization, were all recorded in the questionnaires. Only the 81 children and guardians who provided complete information about their medical conditions in the questionnaire were chosen for further examination. In this study, the patient selection for the three groups (i.e., those with SIRS, those with sepsis, and those who underwent septic shock) was based on tabulation Nelson criteria (11).

Sepsis is SIRS caused by either a suspected or proven infection (11). The clinical spectrum of sepsis includes systemic infection, such as bacteremia or local infection, pneumonia, meningitis, pyelonephritis, etc. Septic shock is defined as severe sepsis associated with persistent hypoperfusion or hypotension for more than an hour, despite adequate fluid therapy and inotropic or vasopressor drug administration (12). Hypotension is defined as a blood pressure less than the 5th percentile according to age or a systolic blood pressure less than the 2nd percentile according to age (12).

One ml blood samples were used to measure PCT levels. For the measurement of CRP and ESR levels, blood cultures and CBC-Diff blood samples were taken by nurses in the necessary amounts at patients' admissions and before imitating antibiotic treatments. Urine cultures and, in specific situations, CSF fluid cultures and LP levels, were also analyzed. Chest radiography was conducted in children suspected of having pneumonia, sepsis, or respiratory problems. In this study, PCT measurements were made quantitatively by employing quantitative electroluminescence (ECL) using the Elecsys BRAHMS PCT kit (Roche, Germany). The serum samples were immediately separated from the blood samples and were stored at -20°C in separate microtubes until the assays were performed.CRP levels were measured with the immunoturbidimetry kits of the PAR's product testing company, while ESR levels were measured using Westergreen. The Kolmogorov-Smirnov test was used to evaluate the distribution of quantitative variables, and the values were expressed as numbers (percentages) or mean $\pm$ standard deviations, as appropriate. Comparisons were performed by ANOVA for normally distributed, and the Kruskal-Wallis test was used for non-normally distributed. The kappa statistic was estimated to indicate the degree of agreement between two variables. All statistical analyses were performed using the SPSS version 16.0 for Windows (SPSS, Chicago, IL, USA).

4. Results

Of the patients, 13 (15.5%) were suspected of having infection, 31 (36.9%) had SIRS, 27 (32.1%) had sepsis, and 10 (11.9%) had undergone septic shock. The most common diseases were pneumonia and encephalitis, seen in 17 (20.2%) and 9 (10.7%) patients, respectively. The serum PCT levels were equal to or less than 0.5 ng/mL in 41.7% of children, 0.5 - 10 ng/mL in 36.9% of children, and more than 10 ng/mL in 20.2% of children. ESR levels were more than 20 in 69% of patients, while 71.4% of patients had serum CRP levels above 10. The mean standard deviations and kappa (π) values of ESR, CRP, and PCT, as well as length of stay in the hospital, in all four of the studied groups are presented in Table 1.

Increased PCT and CRP had moderate consistency (with a kappa coefficient of 46.0) and was significant ($P < 0.0001$), as shown in Table 2. However, the consistency of the increases in PCT and ESR were weak (with a kappa coefficient of 37.0) and significant ($P = 0.001$), as shown in Table 3.

Table 1. Comparison of the Means and Standard Deviations of Variables in the Studied Groups

Variable	Suspected of Infection	SIRS	Sepsis	Septic Shock	P Value
ESR	20.21 ± 4.7	30.39 ± 1.5	37.49 ± 8.7	32.64 ± 4.7	0.011
CRP	22.32 ± 9.3	36.41 ± 9.2	43.51 ± 2.7	31.90 ± 4.7	0.001
PCT	4.1 ± 1.3	7.19 ± 2	6.4 ± 5.6	29.4 ± 1	0.005
Length of administration	8.3 ± 4.4	6.1 ± 2.6	10.6 ± 4.2	18.4 ± 8.4	0.001

In other words, there was a significant difference between these two variables (P = 0.001).

Along with the elevated levels of CRP, ESR was observed to have moderate consistency (with a kappa coefficient of 60.00) and was significant (P < 0.0001), as shown in Table 4.

5. Discussion

The results of our research demonstrated that PCT levels in children with septic shock were significantly higher than those in the other three groups. However, the increases in PCT, CRP, and ESR had a noticeable statistical difference (Table 1). In the present study, a moderate compatibility was observed between the increases in serum PCT and CRP levels (Table 2), whereas there was a weak consistency between the increases in PCT and ESR (Table 3). PCT levels have tangible changes from the beginning of the ailment until its development. Furthermore, since the majority of the patients did not refer to a clinic for diagnoses, treatments, or hospitalization immediately after the commencement of the disease and referred to such places at different times after their disease commenced, their primary serum PCT levels had significant changes from the onset of their disease until its progression. In addition, consuming oral antibiotics might have altered the serum PCT levels and the clinical course of the disease in the children. Therefore, we were unable to determine this factor in our study.

Furthermore, since performing PCT tests is expensive, we avoided repeating testing in the clinical course of the disease. Some strengths of our study include the measurement of PCT using a quantitative method and the exclusion of children treated by intravenous antibiotics prior to hospitalization from the study. Several studies have shown that PCT has a higher sensitivity and specificity compared with CRP and ESR when diagnosing sepsis and septic shock and differentiating both from SIRS. For instance, Ghorbani et al. evaluated serum PCT levels in 100 patients in four groups suffering from SIRS, sepsis, sepsis syndrome, and septic shock. Their findings were similar to ours: 36% of the patients had SIRS, 38% had sepsis, 12% had sepsis syndrome, and 14% had septic shock. They concluded that high serum PCT levels have a significant association with septic shock, positive blood cultures, and unconsciousness; thus, measuring serum PCT levels can play a huge role in differentiating septic shock from SIRS and other types of infections (8). In our study, serum PCT levels in children with SIRS were significantly different than in those in children who underwent septic shock (P = 0.025). However, serum PCT levels in children who had septic shock were considerably different from those in children with septic shock (P = 0.017). Moreover, serum PCT levels in children with septic shock were significantly different from those suspected of having infection (P = 0.011).

Further, Abedini et al. evaluated the changes in PCT, CRP, and ESR levels and the number of white blood cells (WBCs) in the peripheral blood before and three days after the onset of appropriate treatment. Their sample included 50 children aged between 1 and 3 years who were diagnosed with SIRS and admitted to the pediatrics department. They concluded that a good correlation existed between PCT and CRP levels before treatment (CC = 0.66, P = 0.01) and that a moderate correlation existed between PCT and ESR levels before treatment (CC = 0.29, P = 0.04). However, there were no significant correlations between serum PCT levels, serum CRP levels, serum ESR levels, and the number of peripheral blood leukocytes on the third day after the beginning of treatment (13). In our study, ESR levels in children who underwent septic shock were statistically and significantly different from those of children suspected of having infection (P = 0.022). Nevertheless, there were no significant differences in ESR levels between children with septic shock and those with SIRS nor in ESR levels between children affected by septic shock and those with sepsis. Similarly, Barati et al. compared 60 burn patients similar in age, burn percentages, and burn lengths. He studied two groups; in the first, the patients had sepsis symptoms and a proven organism, while the second group had no clinical signs of sepsis. Inflammatory markers, such as PCT, CRP, and ESR levels, and the number of WBCs and peripheral blood neutrophils were measured in both groups. Barati et al. concluded that serum PCT levels in the first group were significantly higher than serum PCT

Table 2. Comparison of PCT and CRP Levels in the Studied Children

PCT	CRP			
	≤ 10 mg/L		> 10 mg/L	
	Percent	Number	Percent	Number
< 0.5 ng/mL	22.9	19	19.3	16
> 0.5 ng/mL	6	5	51.8	43

Table 3. Comparison of PCT and ESR Levels in the Studied Children

PCT	ESR				Total	
	≥ 20 mm/h		< 20 mm/h			
	Percent	Number	Percent	Number	Percent	Number
< 0.5 ng/L	34.6	18	32.7	17	67.3	35
> 10 ng/L	1.9	1	3.8	16	32.7	17
Total	36.5	19	63.5	19	100	52

Table 4. Comparison of CRP and ESR Levels in the Studied Children

ESR	CRP				Total	
	≤ 10 mg/L		10 < mg/L			
	Percent	Number	Percent	Number	Percent	Number
≤ 20 mm/h	21.4	18	9.5	8	31.0	26
> 20 mm/h	7.1	6	61.9	52	69.0	58
Total	28.6	24	71.4	60	100	84

levels in the second group ($P < 0.001$). Furthermore, the CRP and ESR levels and the number of WBCs in the peripheral blood in the sepsis and non-sepsis groups were not significantly different. Therefore, serum PCT was concluded to be a useful laboratory parameter for the diagnosis of sepsis after burning, while the other studied parameters had little value (14). In our study, children with sepsis and those who underwent septic shock had higher serum PCT levels compared with those of children with sepsis or SIRS. In addition, the increase in serum PCT levels was considerably higher than the increase in ESR levels (PCT, $P = 0.005$; ESR, $P = 0.011$).

Moreover, a meta-analysis was conducted on 351 articles published in the Medline database between 1970 and 2002 to evaluate and compare PCT and CRP levels in the diagnosis of bacterial infection in Quebec, Canada in 2004. In total, 46 infants, 638 children, and 702 adults were hospitalized in different hospital wards; half were admitted to ICU wards for further analysis. The sensitivity and specificity of PCT were 0.88 and 0.77, respectively, and those of CRP were 0.81 and 0.67, respectively. The results of this meta-analysis demonstrated that the accuracy of measuring PCT levels was higher than that of measuring CRP levels when it came to differentiating bacterial infection from other infections (15). In our study, due to the low number of samples in each of the four groups, it was not possible to evaluate the sensitivity and specificity of PCT and CRP; consequently, we employed a Kappa coefficient or a correlation coefficient between the two mentioned variables and ESR. The correlation results are presented in Tables 2 and 3. In addition, a study was conducted by Cassado et al. in 2003 that compared PCT and CRP levels and counted the neutrophils in the peripheral blood in children with suspected sepsis. They found that serum PCT is superior to CRP in determining the severity of bacterial infections (2). In our study, PCT levels in children who underwent septic shock increased significantly ($P = 0.005$) compared with those of children with sepsis or SIRS, while elevated CRP levels showed a lower increase ($P = 0.001$) than PCT levels. Therefore, in our study, we concluded that increased PCT levels have more value in differentiating between septic shock and sepsis or SIRS than increased CRP and ESR levels.

Among these three variables, increased ESR levels had the least prognostic value in differentiating the three stages of infection. Since PCT tests are expensive and may not be possible in areas without a substantial medical infrastructure, and due to the existence of moderate consistency between the development of PCT and CRP values in our study, measuring serum CRP levels could be recommended as a second choice for differentiating the three stages of infection.

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Footnotes

Authors' Contribution: Study concept and design, Fardin Asadi; acquisition of the data, Fardin Asadi; analysis and interpretation of the data, Saeideh Mazloomzadeh; drafting of the manuscript, Hasan Pourmoshtagh; critical revision of the manuscript for important intellectual content, Ali Koosha; statistical analysis, Saeideh Mazloomzadeh; administrative, technical, and material support, Hasan Pourmoshtagh; study supervision, Fardin Asadi.

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