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Serum Procalcitonin as a Diagnostic Biomarker for Bacterial Infection in Febrile Children

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Abstract

Introduction and Research Problem: Fever is one of the most common presenting sign of illnesses in pediatric practice. There is no precise test to diagnose bacterial infection rather than blood culture that often has delay results. Our aim is to prove that Procalcitonin is useful in early detection of acute bacterial infection compared to blood culture and CRP in its sensitivity.

Materials and methods: In this prospective cohort study, Any sick patient ranging in age from over 1 month to 18 years of age who have a temperature over 38°C was considered at risk of having bacterial infection and were considered eligible for inclusion. Children with recent surgeries, chronic disease, immunodeficiency or took antibiotic within 10 days of presentation, were excluded. also children with important data insufficiency due to incomplete blood measurements were excluded as well. These patients were screened for bacterial infection and we collected demographic data, vital signs, medical histories, reasons for admission and the available laboratory and radiology test results related to their admission.

Keywords: Procalcitonin; Diagnostic biomarker; Bacterial infection

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Summary of Results

Study sample started with 110 cases, but Total cases included was 62 cases. Mean age of the patient was 3.74 (± 4.14), of which 35(56.5%) was male and 27 (43.5%) was female. 53.2% of patient was having chronic illness affecting different body systems with central nervous system representing 27.7% of cases followed by hematologic disease in 18.2% of cases. Cultures to confirm bacterial infection was done for all patients, 36 cases (58.1%) had a urine culture of which 7 cases (11.3%) was positive, with 4 cases (11.1%). 48 cases (77.4%) had blood culture of which 3 cases (6.3%) were positive.

Gram-negative organisms, 4 cases (11.1%) of positive urine cultures and 2 cases (66.7%) of positive blood culture mostly caused infections. The mean level of PCT was 191.08 (± 557.89). Most cases 36 (58.1%) had normal PCT level and 26 cases (41.9%) had elevated levels.

There was no association between PCT and bacterial infection in urine (P>0.05) or blood infection (P>0.05).

Conclusion and Recommendations

Infections are one of the most common presenting illnesses in healthcare centers worldwide, usually manifesting with fever. One of the struggles in treating infections is finding the cause whether it's viral or bacterial. So, there is a growing evidence base supporting the measurement of procalcitonin (PCT) levels in patients with fever [1]. Proclcitonin is the peptide precursor of calcitonin which is an acute-phase reactant that is produced in response to inflammatory stimuli.

This research showed no association between PCT level and the presence of bacterial infection. This may be due to the small sample size limited by parents' refusal to participate. However, an incidental association was noticed between elevated PCT level and fever which support the literature in proving that PCT level is sensitive for signs and symptoms of infection.

Introduction

Fever is considered a common presenting sign of illness in the pediatric age group [1,2]. Fever can occur due to a self-limited viral infection, inflammatory conditions, such as pancreatitis, or bacterial infection. Under specific situations, it may be difficult to differentiate between bacterial infection, which is a major cause of morbidity and mortality in the pediatric population and other differential diagnoses [3].

This can lead to serious complications from either an untreated bacterial infection, such as meningitis and pyelonephritis, or unnecessary treatment of viral infections and inflammatory conditions with empirical antibiotics, leading to bacterial resistance, allergies, child discomfort and financial cost.

There is no precise test to diagnose bacterial infection other than blood culture, which often has delayed results. Procalcitonin (PCT) is the peptide precursor of calcitonin. It is produced by end peptidase-cleavage in parafollicular C cells of the thyroid inneuroendocrine cells of the lung and intestine and is released as an acute-phase reactant in response to inflammatory stimuli [4]. High levels of procalcitonin during inflammation are associated with bacterial endotoxin and inflammatory cytokines.

Increased levels of serum procalcitonin in response to viral infections and noninfectious inflammatory stimuli are much less pronounced [5,6].

Several studies have shown that Procalcitonin offers better sensitivity and specificity compared to other markers, such as CRP [7,8]. PCT has been confirmed as an excellent marker in the detection of invasive bacterial infections in ED and can detect the presence of a fever in <12 hour.

The objective of this research study was to determine whether Procalcitonin is useful in the early detection of acute bacterial infection.

Methodology

This was a prospective cohort study of children admitted to the emergency department and pediatric ward at King Abdul-Aziz University Hospital, Jeddah, Saudi Arabia from July 2014 to September 2014.

Sick pediatric patients ranging in age from over 3 to 14 years of age with a fever (temperature over 38°C) were considered at risk of having a bacterial infection and were considered eligible for inclusion in the study.

Children with recent surgeries, chronic disease, immunodeficiency or those who took antibiotics within 10 days of presentation were excluded from the study. Children with data insufficiency due to incomplete blood measurements were also excluded.

All of the parents of the participants were asked to read and sign an informed written consent to participate in the study. The study and the informed consent were approved by the Research Ethics Committee of King Abdul Aziz University Hospital of Medical Sciences, Jeddah.

Patients were screened for bacterial infection by obtaining blood samples for cultures, CBC, CRP and PCT. Blood samples were collected in EDTA by venipuncture. The blood cultures were immediately established, and the leukocyte count was determined automatically by the hospital laboratory. Serum CRP was determined by nephelometry. PCT was determined from frozen samples (-20°C) using an immunoluminometric assay. Urine culture was obtained from either a catheterized sample or mid-stream urine in toilet-trained children.

We collected the following demographic data: vital signs, medical histories, reasons for admission and available laboratory and radiology test results related to the patients' admissions. All of the laboratory and radiology tests were ordered by the hospital staff and were performed at the hospital except for the PCT samples, which were immediately frozen for subsequent determination in a laboratory outside the hospital.

Statistical analysis: we use SPSS version 20. Chi square and Fischer exact and chi square test for comparison of mean, P-value consider significant if <0.05.

Results

The study samples originated from 110 cases. The response rate was 63%, and refusal from the parents was due to harmful blood withdrawal, which contributed to the exclusion of 40 cases (Figure 1). After laboratory analysis, the PCT values of 8 cases were missed and were also excluded.

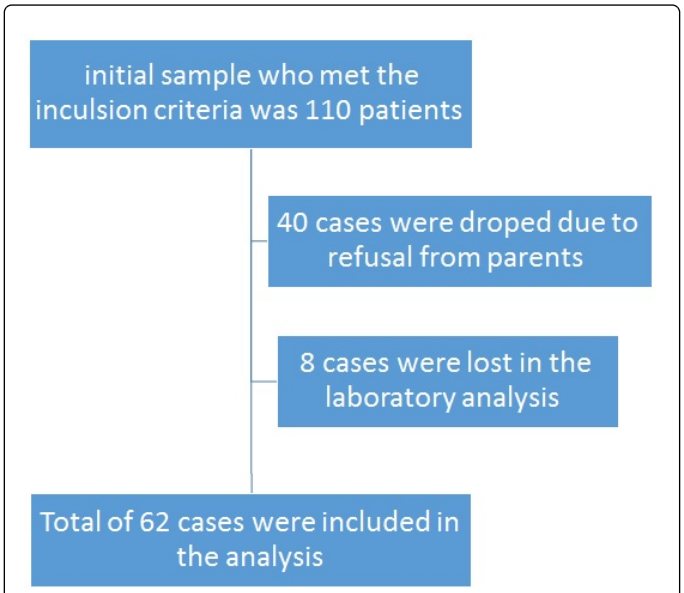

Figure 1: The flow chart of the laboratory analysis.

A total of 62 cases were included in the study, of which 35 (56.5%) cases were male and 27 (43.5%) cases were female with a mean age of 3.74 (± 4.14) months. Chronic conditions were affecting 33 patients (53.2%), with involvement of the central nervous system in 9 cases (27.7%), followed by hematologic disease in 6 cases (18.2%).

At the time of blood withdrawal, the clinical picture of the patients showed a mean of 37.85 (± 0.94), 139.03 (± 23.57), 23.83 (± 10.37) and 97.34 (± 5.42) for temperature, heart rate, respiratory rate and oxygen saturation, respectively.

Blood, urine and CSF cultures were performed for all patients to confirm bacterial infection in 48 cases (77.4%), 36 cases (58.1%), and 16 cases (16.1%), respectively. Infection was confirmed in 7 urine

cultures (19.4%) and 3 blood cultures (6.3%), the main bacteria was Gram-negative organism in 4 cases (11.1%) of urine cultures and 2 cases (66.7%) of blood culture. The mean level of PCT was 191.08 (± 557.89). Thirty-six cases (58.1%) had normal PCT levels and 26 cases (41.9%) had elevated levels.

The PCT level was not an indicator for bacterial infection in urine (P=0.63) or blood (P=0.06) (Table 1). Regarding other markers for infection, such as WBC count and CRP (p=0.179), there was no association. However, there was a significant relationship (P=0.007) between PCT level and high temperature (>39oC).

	Mean (± SD)	**Significance**
Age in years	3.74 (± 4.14)	
Temperature	37.8 (± 0.9)	P=0.019
White blood cells count		P=0.148
	Frequency (%)	Significance
Gender		
Male	35 (56.5%)	P=0.463
Female	27 (43.5%)	
Patients with chronic illness		
yes	33 (53.2%)	P=0.085
no	29 (46.8%)	
Patients PCT levels		
Normal level	36 (58.1%)	
Elevated level	26 (41.9%)	
Urine culture results		
negative	29 (80.8%)	P=0.633
positive	7 (19.4%)	
blood culture results		
negative	45 (93.8%)	P=0.066
positive	3 (6.3%)	
CSF culture results		
Negative	10 (100%)	
positive	0 (0%)	

Table 1: Patient characteristics and significance with procalcitonin results.

Discussion

Urgent diagnosis and treatment are required in bacterial infection, particularly in the pediatric age group. The need for a sensitive and specific diagnostic biological marker for bacterial infection is increasing in order for appropriate and early management steps to be performed in a timely manner. The biological kinetics of PCT makes it a suitable diagnostic marker in the early diagnosis of bacterial infection. PCT secretion begins within 4 h after stimulation and peaks at 8 hour, clearing when the insult is under control. PCT is stable in serum samples, and the assay is relatively easy to perform with a moderate cost. The result is available within 2 hour. Although the cost of performing an assay to determine PCT levels is affordable for other inflammatory markers, such as CRP, the higher accuracy of PCT is sufficient for consideration for widespread use in clinical practice [9].

PCT has been examined in several studies in the literature, and has been demonstrated as an indicator specific for bacterial infections.

In a study performed in the Pediatric Rheumatology Unit at Christian Medical College, in India, 16 patients were known to have systemic lupus ethyrhmatosis (11 patients in the disease flare group and 5 patients in the infection group). The mean PCT was 92.2 ng/ml in the SLE infectious group and 3.50 ng/ml in the SLE flare group, which was statistically significant (p=0.009). This study concluded that high PCT levels (>1.2 ng/ml) in febrile SLE patients attributed fever to bacterial infection rather than an inflammatory process related to a flare-up of the disease [9,10].

In addition to its accuracy as a diagnostic marker for bacterial infection, serum PCT can play a role in the prediction of renal parenchymal involvement (RPI) in children diagnosed with urinary tract infections. This was shown in a meta-analysis of prospective clinical studies [11]. PubMed and the Cochrane Central Register of Controlled Trials was searched for prospective studies involving children with culture-proven UTIs. Additional eligibility criteria were the measurement of serum PCT at presentation and performance of DMSA scintigraphy within 14 days. All studies were prospective cohort studies and included a total of 627 patients (68% female) with culture-proven UTIs. The study concluded that children with culture-proven UTI and a serum PCT value >0.5 ng/mL predicted reasonably well the presence of RPI, as evidenced by DMSA scintigraphy. In conclusion, PCT may help to identify children with UTI who would thus require further evaluation and management.

Serum procalcitonin can also serve as a diagnostic marker for bacterial infection in pediatric patients with febrile neutropenia. A systemic review and meta-analysis in China, which includes a total of 10 studies examining PCT tests and 8 studies examining CRP tests, were included in the final analysis. The prevalence of bacterial sepsis was 304 out of 1031 (29.5%) in PCT studies and 741 out of 1316 (56.3%) in CRP studies [12]. PCT had a greater likelihood ratio positive (2.50; 95% CI: 1.64-3.81) for the prediction of bacterial sepsis rather than serum CRP. However, each included study used its own best cutoff value, and the linear regression methods used in the analysis may have led to potential threshold differences between studies.

Another meta-analysis study involving 7 studies and 2317 febrile infants showed that serum PCT can be a reliable predictor marker for bacterial sepsis in febrile young infants.

In contrast to another study, a study performed at the University of Pennsylvania showed that the area under the receiver operating characteristic curve was similar for PCT (0.73, 95% CI 0.69, 0.77) and CRP (0.75, 95% CI 0.71, 0.79; P=0 .36), but both outperformed WBC, ANC, and % immature neutrophils (P<0.01 for all pairwise comparisons) [13,14]. This study concluded that peak blood PCT measured close to PICU admission was not superior to CRP in differentiating severe bacterial infection from viral illness and sterile inflammation.

In our study, we did not identify any association between elevation of serum PCT and positive bacterial culture. However, positive blood culture was found only in 6.3% of the patients and thus makes the comparison statistically difficult.

In addition, there was an incidental, although statistically significant, association between the temperature and level of elevation of PCT, which is consistent with published findings in the literature that PCT levels increase proportionally with an increase in signs and symptoms of infection.

Limitations

Our study has several limitations, including a relatively small sample size and including only a single center in Saudi Arabia. In addition, we could not address the other contributing factors, such as major burns, severe trauma, acute multi organ failure, major abdominal or cardiothoracic surgery and noninfectious systemic inflammatory response associated high PCT. In addition, 37% of the sample withdrew from the study due to concern over blood withdrawal despite medical assurance. Another limitation is that only 3 blood cultures (6.3%) of the collected samples were positive, which may have skewed the results.

We propose future studies with a larger sample size from multiple centers in order to have a more representative pediatric population and to address all the potential confounding factors that might attribute to the changes observed in serum PCT.

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