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Original Article

Presepsin: A new marker of catheter related blood stream infections in pediatric patients☆

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ABSTRACT

Background: Catheter related blood stream infections (CRBSI) are mostly preventable hospital-acquired conditions. We aimed to investigate the value of presepsin in detection of CRBSI in hospitalized children.
Methods: Hospitalized pediatric patients who had clinical suspicion of CRBSI were followed. Results of peripheral blood cultures and blood cultures from central venous catheters, procalcitonin (PCT), C-reactive protein (CRP), total white blood cell (WBC) counts were recorded. Serum samples for presepsin were studied at the same time with the samples of healthy controls. The patients with positive blood cultures were defined as proven CRBSI and with negative cultures as suspected CRBSI.
Results: Fifty-eight patients and 80 healthy controls were included in the study. Proven CRBSI group consisted of 36 patients (62%) with positive blood cultures and compared with the suspected CRBSI group (n = 22, 36%) with negative culture results. There was no difference between proven and suspected CRBSI groups concerning WBC, PCT, CRP and presepsin. Presepsin was significantly higher in patient groups when compared with healthy controls. The receiver operating characteristic curve area under the curve was 0.98 (%95 CI: 0.97–1) and best cut-off value was 990 pg/ml.
Conclusion: In hospitalized pediatric patients with CRBSI, presepsin may be a helpful rapid marker in early diagnosis.

1. Introduction

Catheter related blood stream infections (CRBSI) are mostly preventable hospital-acquired conditions that contribute substantially to morbidity, mortality and health care costs in all age groups and diagnoses [1,2]. Most nosocomial bloodstream infections among pediatric patients are related to the use of an intravascular device. In United States, current estimates suggest between 15,000 and 41,000 CRBSI occur per year in non-neonatal hospitalized patients [3].

Clinical findings are unreliable for establishing the diagnosis of CRBSI because of their poor sensitivity and specificity. The most sensitive clinical finding, fever, has poor specificity. Inflammation or purulence around the insertion site has greater specificity but poor sensitivity [4,5]. Laboratory criteria for diagnosing CRBSI are precise, but differences in definitions and methodologies among various studies have made data difficult to compare [4,6]. Earlier diagnosis may offer the ability to initiate treatment to prevent adverse outcomes. Immediate recognition of signs and introduction of proper treatment can improve the prognosis.

Cluster of differentiation 14 (CD14) is one of the leucocyte differentiation antigens. CD14 exists in macrophages, monocytes, granulocytes and their cell membranes. It serves as a receptor of the lipopolysaccharide (LPS)-LPS binding protein complexes and activates a series of signal transduction pathways and inflammatory cascades against microorganisms [7–10]. CD14 has two forms, namely a membrane bound CD14 and soluble CD14 (sCD14). During inflammation, in blood sCD14 is cleaved by proteases and a truncated form sCD14 subtype is generated which is called presepsin [11]. Hence, the levels of presepsin in blood may be a reflection of systemic inflammation. After detection of its value as a new

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biomarker of inflammation, it has been reported in many studies for the prediction of sepsis. Following meta-analysis showed that it has a moderate diagnostic accuracy in differentiating sepsis from non-sepsis [12,13].

In general, fever, leukocytosis and elevated acute phase reactants, such as C-reactive protein (CRP), are commonly used to evaluate for CRBSI and serve as important determinants for the empiric initiation of antimicrobial therapy. The aim of the present study was investigation of value of presepsin to detect CRBSI in hospitalized children.

2. Materials and methods

2.1. Patient selection

The study was conducted in the Hacettepe University Ihsan Dogramaci Children's Hospital, Ankara, Turkey, between October 2013 and June 2015. This hospital has 270 beds and serves as a referral tertiary hospital with about 11,000 inpatients per year. This trial was approved by the ethical committee of the Zekai Tahir Burak Maternity Teaching Hospital, Ministry of Health, Ankara (Approval number: 26). Patients were enrolled in the study after written parental consent.

Pediatric patients who had clinical suspicion of CRBSI and were followed by pediatric infectious disease specialists in in-patient clinics of Hacettepe University Ihsan Dogramacı Children's Hospital. Patients who were between 1 month and 18 years of age and displayed clinical signs of CRBSI were enrolled in the study. Healthy controls were individuals who had admitted to our hospital for well-child care visits without an underlying disease. They were not hospitalized. These children were free of infection and any other kind of diseases.

2.2. Definitions

Clinical suspicion of a CRBSI was based on the onset of features suggestive of infection; clinical manifestations of infection (fever, chills, and/or hypotension, e.g.), central venous catheter being in place for more than 48 h, and no other apparent source of infection [14]. For suspected CRBSI, paired blood samples from catheter and a peripheral vein were obtained and cultivations were implemented [1]. Patients were excluded from the study if they had received antibiotics within the previous 24 h of presentation with fever, because studies have shown that presepsin levels decrease in time with antibiotic treatment [15]. If a patient had more than one episodes of suspected CRBSI during the study period, only the first episode was included in the study.

2.3. Study protocol

At the time of suspicion of CRBSI with the clinical findings, peripheral blood cultures, blood cultures from central venous catheters and whole blood samples were obtained. In addition to demographic characteristics of patients (age, gender, underlying diseases), results of peripheral blood cultures and blood cultures from central venous catheters and total white blood cell (WBC) counts were recorded.

Patients with suspected CRBSI (Group 1) were further divided into two subgroups based on whether they had proven (Group 1a: patients with positive blood cultures, clinical findings in agreement with the diagnosis) or suspected (Group 1b: patients with clinical findings of CRBSI, but with negative blood cultures). The control group (Group 2) consisted of age matched healthy children who had no underlying diseases and were admitted to our center for well-child care visits.

2.4. Laboratory analysis

Whole blood samples were collected and serum samples were stored at −80° C for detection of C-reactive protein (CRP) levels, procalcitonin (PCT) levels and presepsin levels. These parameters were studied all together at the end of inclusion of all subjects. CRP was measured by nephelometric methods. Levels of PCT were determined using the Brahms Kryptor compact immunoassay analyzer (Berlin, Germany).

Presepsin levels were measured by Human Presepsin ELISA (Aviscera Bioscience, Inc., CA, USA). This kit employed the quantitative sandwich enzyme linked immunoassay assay format. The plate was pre-coated with an antibody specific for human soluble CD14 subtype. The capture antibody could bind to human soluble CD14 subtype in the standard and samples. After washing the plate of any unbound substances, a biotinylated antibody against human soluble CD14 subtype was added to the wells. After another washing of the plate, Streptavidin-horseradish peroxidase conjugate was added. After the last wash to remove any unbound enzyme, a substrate solution was added to the wells and color developed in direct proportion to the amount of human soluble CD14 subtype bound in the standard solutions and samples. A standard curve was established and sample values were read off the standard curve. Presepsin levels of patients were compared with healthy controls. PCT, CRP levels and WBC counts were compared within the patient group.

2.5. Blood culture

Blood cultures were performed on patients who were suspected for CRBSI. Blood cultures were not taken from healthy controls. The Bactec microbial detection system (Becton-Dickinson, Sparks, MD) was used to detect positive blood cultures.

2.6. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics (Windows, Version 22.0. Armonk, NY: IBM Corp.) Descriptive statistics were used to summarize the participants' baseline characteristics, including medians, minimum and maximum values for continuous variables and frequency distributions for categorical variables.

The normality of quantitative variables was tested by Kolmogorov-Smirnov test. For continuous variables, the independent-groups *t*-test was used for normally distributed variables or the nonparametric Kruskall wallis test, if the normality assumption was violated. The area under the receiver operating characteristic (ROC) curve was calculated to evaluate the diagnostic significance of the tested parameters. Data were expressed as area under ROC curves with 95% confidence intervals (CIs). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also calculated. In all analyses, two-tailed *p*-values <0.05 were regarded as statistically significant.

3. Results

A total of 58 patients fulfilling the criteria for a diagnosis of suspected CRBSI were enrolled in the study, 36 (62%) of which had proven CRBSI (Group 1a) and 22 (38%) had suspected CRBSI (Group 1b). The control group (Group 2) consisted of 80 healthy controls. The demographic characteristics of the study population have been summarized in Table 1. In Group 1, microbiological culture of the urine and chest X-ray were all negative. There were no differences between patient and healthy control groups on the basis of age and gender. Most common underlying diseases were hematologic

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