Journal of Clinical Neuroscience 21 (2014) 1153–1158

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical Study

Serum levels of procalcitonin as a biomarker for differentiating between sepsis and systemic inflammatory response syndrome in the neurological intensive care unit

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ARTICLE INFO

Article history:
Received 30 July 2012
Accepted 25 September 2013

Keywords:
C-reactive protein
Glasgow Coma Scale
Neurological intensive care unit
Procalcitonin
Sepsis
Systemic inflammatory response syndrome

ABSTRACT

We explored the value of procalcitonin (PCT) to differentiate sepsis from systemic inflammatory response syndrome (SIRS), and determine sepsis severity in the neurological intensive care unit (NICU). Blood samples were measured for C-reactive protein (CRP) and PCT levels upon NICU admission, on the day of diagnosis of SIRS or sepsis, and at 3 and 7 days after diagnosis. We found that there were significant differences in serum levels of CRP and PCT as well as Glasgow Coma Scale (GCS) score upon admission between the SIRS and sepsis groups ($p < 0.05$). CRP and white blood cell levels were not significantly different when attempting to differentiate sepsis severity ($p > 0.05$). Multiple comparisons showed that significant differences in serum PCT levels were observed between sepsis and severe sepsis groups, as well as sepsis and septic shock groups ($p < 0.05$). We obtained the highest sensitivity and specificity for SIRS and sepsis with cut-off values of 2 ng/mL for PCT, 44 mg/dL for CRP, and 4 for the GCS. There were no differences in CRP and PCT levels between cerebrovascular disease and non-cerebrovascular disease groups ($p > 0.05$). No differences were found between viral and bacterial meningitis groups ($p > 0.05$). PCT levels are valuable in discriminating sepsis from SIRS and determining sepsis severity in critically ill patients with neurological disease.

1. Introduction

Systemic inflammatory response syndrome (SIRS) is commonly seen after neurological disease in the neurological intensive care unit (NICU). If SIRS is due to infection, the diagnosis is sepsis. Sepsis has a worse prognosis than SIRS, with significant morbidity and mortality [1]. Hence, the diagnosis of sepsis warrants specific and rapid therapy involving early administration of antibiotics and control of the source of sepsis [2]. Differentiating between sepsis and SIRS is important.

Monitoring of the parameters of infection (for example, body temperature, heart rate, respiratory rate, leukocyte count, C-reactive protein [CRP] concentration) is routinely undertaken. However these parameters often provide information that is inadequate for discrimination between SIRS and sepsis. Blood culture is a very specific and confirmatory method for the detection of septicemia. However, test results are not available within 24 hours, and the sensitivity of blood cultures is low [3]. A rapid and reliable test for the discrimination of SIRS and sepsis in the NICU would therefore be very useful.

Procalcitonin (PCT) is the pro-hormone of calcitonin. During sepsis, endotoxins, exotoxins, and cytokines from bacteria stimulate the release of PCT from extra-thyroidal sources (including monocytes and macrophages). Multiple clinical studies have analyzed CRP- and PCT-based diagnoses of sepsis and SIRS [4–8]. Those studies found that serum concentrations of PCT were directly related to infection severity, and that the PCT level served as a more sensitive marker than CRP level or leukocyte count for evaluating the severity and progression of sepsis [6,9–13]. Uzzan et al. undertook a meta-analysis of 49 studies and concluded that the PCT level was superior to CRP level in differentiating between sepsis and SIRS, and they favored the routine measurement of the PCT level to help differentiate between SIRS and sepsis [14]. Tang et al., however, reviewed 18 studies involving 2097 patients. They concluded that the PCT level could not reliably differentiate sepsis from other causes of SIRS. They argued against routine measurement of the PCT level to differentiate sepsis from SIRS [10].

Unfortunately, most studies have focused mainly on intensive care unit (ICU) patients undergoing medical or general surgical interventions. Data on patients with neurosurgical or neurological

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http://dx.doi.org/10.1016/j.jocn.2013.09.021

disease are very limited. Additionally, infection in patients in NICU has its own set of characteristics. It is more difficult to differentiate SIRS and sepsis for patients in the NICU, particularly as body temperature, pulse, respiratory rate, white blood count (WBC), organ function, and tissue perfusion are typically abnormal in the NICU setting.

The objective of this retrospective study was to determine the utility of measurement of serum PCT levels for differentiating between sepsis and SIRS in critically ill patients with neurological disease.

2. Methods

This retrospective study was performed from July 2009 to July 2011, in the 10 bed NICU of a 2225 bed university teaching hospital. Ethical approval was obtained from the hospital, and written informed consent was obtained from every patient.

2.1. Patients and study design

All consecutive patients who exhibited sepsis or SIRS and stayed for >72 hours in the NICU were considered for inclusion in this study. According to our standard definition, patients were defined as having SIRS if they exhibited at least two of the following four criteria: (1) fever (>38 °C) or hypothermia (<36 °C); (2) tachypnoea (>20/minute); (3) tachycardia (>90/minute); or (4) leucopenia (<4.0 × 109/L), leukocytosis (>12.0 × 109/L) or a leftward shift (>10% immature granulocytes). If SIRS was accompanied by bacterial infection, as proven by cultures or on clinical grounds, the patient was defined as having sepsis. The severity of sepsis was evaluated using the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (ACCP/SCCM) definition. Sepsis was defined as infection plus systemic manifestations of infection. Severe sepsis was defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion. Sepsis-induced hypotension was defined as a systolic blood pressure <90 mmHg or mean arterial pressure <70 mmHg or a systolic blood pressure decrease <40 mmHg or <2 standard deviations (SD) below normal for age in the absence of other causes of hypotension. Septic shock was defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation. Sepsis-induced tissue hypoperfusion was defined as septic shock, an elevated lactate, or oliguria [15–17].

The exclusion criteria were patients aged <15 years, those with missing data or lost to follow-up, or patients with a medical condition that could affect PCT kinetics (such as chronic renal insufficiency, thyroid disease, or chronic hepatic disease).

Patients were divided into four groups: sepsis, severe sepsis, septic shock, and SIRS. Blood samples for measuring levels of CRP and PCT were taken upon NICU admission, the day of the diagnosis of SIRS or sepsis, and at 3 and 7 days after the diagnosis of SIRS or sepsis, all in the NICU. Demographics, diagnoses, clinical and laboratory findings, and duration of pre-existing mechanical ventilation were recorded.

2.2. Measurement of PCT

A semi-quantitative method based on immunochromatographic principles (BRAHMS PCT-Q kit; Diagnostica GmbH, Hennigsdorf, Germany) was employed to determine PCT concentration. The test uses a monoclonal mouse anti-catacalcin antibody conjugated with colloidal gold (tracer) and a polyclonal sheep anti-calcitonin antibody (solid phase). After the patient sample has been applied to the test strip, the tracer binds PCT to form a marked antigen–antibody complex. This complex moves by means of capillary action through the test system and, in the process, passes through the area containing the test band. Here, the marked antigen–antibody complex binds to the fixed anti-calcitonin antibodies and forms a sandwich complex. At a PCT concentration $\geqslant$0.5 ng/mL, the sandwich complex is visible as a reddish band. Color intensity is directly proportional to PCT concentration. After 30 minutes of incubation at room temperature the color can be related to varying PCT concentration ranges with a reference card. The reference card chosen for this study contained color blocks with the following four PCT concentration ranges: <0.5 ng/mL, $\geqslant$0.5 ng/mL, $\geqslant$2 ng/mL and $\geqslant$10 ng/mL.

2.3. Measurement of CRP

Fasting blood samples for CRP measurement were drawn, and determined by a fully automated IMMAGE Immunochemistry System (Beckman Coulter, Pasadena, CA, USA). The IMMAGE CRP assay is based on the highly sensitive near infrared particle immunoassay method. An anti-CRP antibody-coated particle binds to CRP in the patient sample resulting in the formation of insoluble aggregates causing turbidity. The rate of aggregate formation is directly proportional to the concentration of CRP in the sample. The analytical range for the IMMAGE system was 0.2 mg/L to 1440 mg/L.

2.4. Statistical analyses

Descriptive data were reported as mean ± SD. For statistical analyses, we used the Statistical Package for the Social Sciences version 13.0 (SPSS, Chicago, IL, USA). $p < 0.05$ was considered significant. The PCT level, CRP level, WBC count and the Glasgow Coma Scale (GCS) score at hospital admission were adopted to compare the usefulness of different markers and patient characteristics in differentiating between SIRS and sepsis. We used Student's *t*-test for continuous variables and Mann–Whitney U test for categorical variables. Comparison among different sepsis grades was carried out only in patients with sepsis; data upon NICU admission, the day of the diagnosis of sepsis, 3 days after the diagnosis of sepsis, and 7 days after the diagnosis sepsis were used. Analysis of variance for continuous variables and the Kruskal–Wallis test for categorical variables were used. Sensitivity and specificity, as well as positive and negative predictive values were calculated, and a receiver-operating characteristic (ROC) curve created.

3. Results

A total of 104 patients were included in the study; 56 with sepsis and 48 with SIRS. Fourteen patients had viral encephalitis (13.46%), three had purulent meningitis (2.88%), two had cryptococcal meningitis (1.92%), 57 had cerebrovascular disease (54.81%), three had multiple sclerosis (2.88%), nine had systemic lupus erythematosus (8.65%), two had Guillain Barré syndrome (1.92%), five had metabolic encephalopathy (4.81%), three had epilepsy (2.88%), five had tubercular meningitis (4.81%), and one had hypoxic ischemic encephalopathy (0.96%). Patient baseline characteristics are summarized in Table 1. To compare the usefulness of serum levels of CRP and PCT in differentiating sepsis from SIRS, we recorded the values of CRP and PCT upon NICU admission, the day of diagnosis, and at 3 and 7 days after the diagnosis of SIRS or sepsis.

Upon NICU admission, patients with sepsis had significantly higher serum levels of CRP and PCT in comparison with patients with SIRS ($p < 0.05$; Table 2). The mean concentration of CRP was 34.41 ± 34.45 mg/dL in SIRS patients, and 76.87 ± 72.39 mg/dL in sepsis patients. The Mann–Whitney U test derived value of PCT was 541.00 ($p < 0.05$; Table 2). The GCS score was also significantly different between these two groups ($p < 0.05$; Table 2). Patients with sepsis had a lower GCS score, with a mean of 8.05 ± 2.89, compared