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Reduction in procalcitonin level and outcome in critically ill children with severe sepsis/septic shock—A pilot study☆,☆☆

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ABSTRACT

Purpose: To investigate if reduction in procalcitonin (PCT) provides useful information about 28-day mortality in children with severe sepsis or septic shock.
Materials and Methods: Design: Prospective observational study. Setting: Mixed adult-pediatric intensive care unit in a teaching hospital. Subjects: Children up to 18 years of age admitted with severe sepsis or septic shock between March 2011 and June 2013. Procalcitonin measured using electrochemiluminescence immunoassay on the day of admission with sepsis (D0) and 72-96 hours later (D4). Reduction in PCT from D0 to D4 correlated with the primary outcome, that is, 28-day mortality.
Results: Twenty-five children of median age of 14 years (range, 6-18 years) were included, but 5 died before D4 after admission. Six of the remaining 20 children died between D4 and D28, and 14 survived to D28. At admission, the median of the Pediatric Risk of Mortality III score was 10 (interquartile range [IQR], 5-16) and that of the Sequential Organ Failure Assessment score was 11 (IQR, 7-15). The median PCT level was 9.7 ng/mL on D0 ($n = 25$) and 3.3 ng/mL on D4 ($n = 20$). On D0, the median PCT level was 25.0 ng/mL in the 14 survivors and 8.4 ng/mL in the 11 nonsurvivors ($P = .075$). On D4, the median PCT level was 3.1 ng/mL in the 14 survivors and 4.5 ng/mL in the 6 nonsurvivors who lived to D4 ($P = .71$); the reduction in PCT (D0 minus D4) was 17.3 ng/mL (IQR, 3.5-38.0 ng/mL) in the survivors and −1.1 ng/mL (IQR, −24.9 to 8.6 ng/mL) in the 6 nonsurvivors ($P = .017$). Percent reduction in PCT (100 * [D0 − D4]/D0) was 75.5% (IQR, 54.8%-80.7%) in the survivors and −200.3% (IQR, −937.8% to 42.4%) in the 6 nonsurvivors ($P = .006$).
Conclusion: This small pilot study suggests that further studies are indicated to determine whether children with severe sepsis or septic shock are less likely to die if they have a reduction in PCT more than 50% in the first 4 days in intensive care.

1. Introduction

Serious infections are a common cause for intensive care unit (ICU) admission in children, especially in developing countries. It is important to identify prognostic factors early as this may necessitate modification of further management. Procalcitonin (PCT) is a precursor of the hormone calcitonin, and is increased early in sepsis and falls rapidly with therapy [1]. Hence, it is a promising biomarker.

Although there is a sizeable literature about the role of PCT in adult ICU patients, the same is not true in children. Procalcitonin has been used in the pediatric population to differentiate sepsis from other nonseptic causes of fever/systemic inflammatory response syndrome in various settings such as emergency department, postcardiac surgery, burns, and so on [2-6]. Procalcitonin-guided antibiotic therapy in the ICU has been found to be safe and decreases the duration of antibiotics in adults; unfortunately, such literature is scarce in children [7]. Recently, change in PCT has been postulated to be a useful marker to identify the prognosis of patients with severe sepsis [8-11]. In this pilot study, we explored the hypothesis that reduction in PCT level is associated with a favorable prognosis in children with severe sepsis or septic shock.

2. Methods

This was a prospective observational study in a tertiary care hospital in a mixed ICU which caters to adults and children. Consecutive children (≤18 years old) admitted with severe sepsis or septic shock were enrolled after obtaining written informed consent from the parents/guardians. Severe sepsis and septic shock were defined as per the international pediatric sepsis consensus conference definitions [12]. Demography, details related to the presenting infection, severity of

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illness, relevant investigations, cultures, and management were noted. The patients were followed up till 28 days after ICU admission and the status on day 28, that is, death or discharge, was the primary outcome. The study was approved by the institutional ethics committee.

Two milliliters of blood was collected from the patient soon after admission (D0), and a repeat sample was obtained after 72 to 96 hours (D4). Serum was separated and stored at −80°C for further analysis. Procalcitonin estimation was done using the commercially available electrochemiluminescence immunoassay (BRAHMS PCT kit, Roche, Henningsdorf, Germany) using a Cobas e411 analyzer with a sensitivity of less than 0.02 ng/mL and a measuring range of 0.02 to 100 ng/mL. Values above 100 ng/mL were not tested further and analyzed assuming them to be 100 ng/mL.

2.1. Statistical analysis

The statistical software SPSS 16 was used for statistical analysis (SPSS, Chicago, Ill). Children who survived till 28 days were considered as "survivors." Comparison between survivors and nonsurvivors was done using nonparametric tests. Receiver operating characteristic curves were constructed to identify the reduction in PCT which differentiated survival from mortality. Significance level was taken at $P < .05$.

3. Results

Between March 2011 and June 2013, 25 children with severe sepsis or septic shock were admitted. The median age was 14 years (interquartile range [IQR], 9.5 to 16.5 years); 21 were male and 4 female; 22 were medical and 3 were surgical; and 9 were admitted from emergency, 9 from another ICU, and 7 from a ward. Sepsis was community acquired in 17 and nosocomial in 8; 4 had severe sepsis and 21 had septic shock. The source of sepsis was gastrointestinal in 12, pneumonia in 9, tropical infections in 4, skin and soft tissue in 3, and miscellaneous in 6. The most commonly affected organ systems were respiratory (21), cardiovascular (22), renal (12), hematologic (10), and neurologic (8). No organisms were isolated from 8 children; organisms were gram positive in 8, gram negative in 6, mixed in 1, and fungal in 1; and possible contamination was found in 1.

Among these children, 5 died before D4. Six of the remaining 20 children died between D4 and D28. The median admission Pediatric Risk of Mortality III score was 10 (IQR, 5-16) and the Sequential Organ Failure Assessment score was 11 (IQR, 7-15); the latter was significantly lower among survivors as compared with nonsurvivors (median [IQR], 7.5 [5-10.3] in survivors and 15 [11-17] in nonsurvivors, $P < .01$) The median length of ICU stay was 8 days (IQR, 5.5-20 days) and that of hospital stay was 18 days (IQR, 7-28.5 days).

All children received organ support; 24 received mechanical ventilation for a median of 6 days (IQR, 3-8 days) and vasoactive agents for a median duration of 4 days (IQR, 2-5 days), 9 received renal replacement therapy, and 19 received transfusion of at least 1 unit of any blood product. Of the 19 children who received transfusions, 13 received packed red blood cell transfusion(s), 16 received fresh-frozen plasma transfusion(s), and 13 received platelet transfusion(s). Antibiotics were administered for a median of 15 days (IQR, 5.5-28 days).

Individual values of PCT on D0 and D4 are shown in Fig. 1. The median PCT level in the entire cohort was 9.65 ng/mL (IQR, 2.97-45.36 ng/mL) at admission (D0); with values of 24.96 ng/mL in the 14 survivors and 8.39 ng/mL in the 11 nonsurvivors ($P = .075$). After 72 to 96 hours (D4), this decreased to 3.34 ng/mL (IQR, 1.18-18.31 ng/mL): 3.11 ng/mL in the 14 survivors and 4.49 ng/mL in the 6 nonsurvivors who survived to D4 ($P = .71$). Comparing these with the other variables traditionally measured in patients with sepsis, total leukocyte count, central venous oxygen saturation, and pH were similar at admission in both groups, whereas the base excess and lactate were significantly higher in nonsurvivors as compared with survivors (Table 1).

We estimated the reduction in PCT level from D0 to D4 (D0 minus D4): a positive value implying a fall and a negative value implying a rise in the PCT level. A median reduction of 7.47 ng/mL (IQR, 0.23-27.51 ng/mL) was seen in the study patients with values of 17.34 ng/mL in the 14 survivors and −1.06 in the 6 nonsurvivors ($P = .017$; Table 1). Percentage reduction in PCT (100 * [D0 − D4]/D0) was also estimated. The median percent reduction in PCT was 70% (IQR, −125.9 to 77.6) for all patients: 75.5% in survivors and −200.3% for the 6 nonsurvivors ($P = .006$). Change in other sepsis variables was not statistically significant. The number of deaths was too small to provide a useful estimate of the area under the receiver operating characteristic curve for reduction in PCT level to predict survival. However, an absolute reduction of PCT of at least 4 ng/mL or a percentage reduction of at least 50% in the first 4 days of ICU stay predicts survival with a sensitivity of 78% and a specificity of 83%.

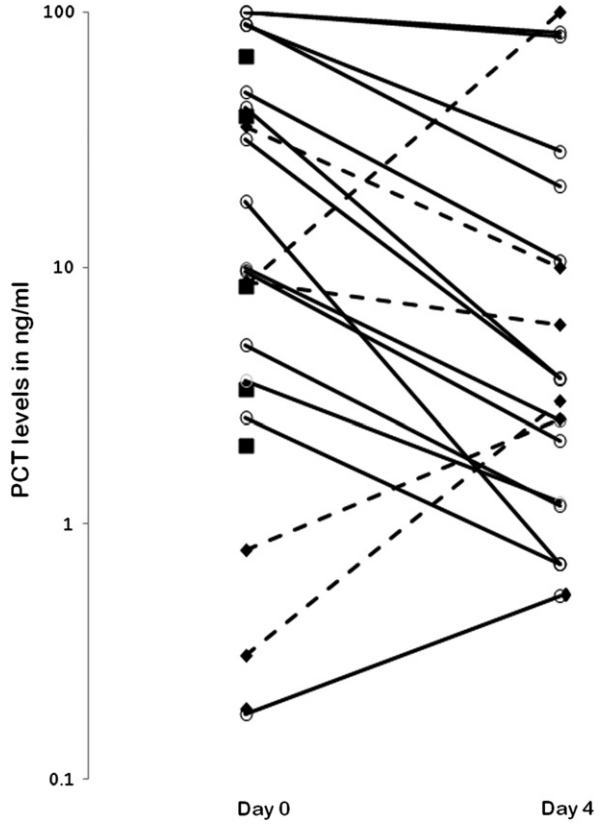

Fig. 1. Procalcitonin values of individual patients on D0 and D4 (on a logarithmic scale): open circles and continuous lines for survivors, solid diamonds and dotted lines for nonsurvivors, and solid squares for the 5 children who died before D4 and have a single value each on D1.

4. Discussion

We prospectively evaluated the change in PCT level as a prognostic indicator in children with severe sepsis and septic shock and found that a significant reduction in PCT is associated with a favorable outcome.

Several studies in children have evaluated the role of PCT to differentiate bacterial infections from other causes of fever [1-5]. Procalcitonin has consistently performed better than C-reactive protein in this scenario, but has its limitations. Similarly, PCT has been used in differentiating sepsis from systemic inflammatory response syndrome in various settings including postoperative cardiac surgery, burns, and extracorporeal membrane oxygenation [1,5-6]. However, its role in such situations has not been proven unequivocally.

Early elevation of PCT has been used to assess the prognosis in some pediatric studies. In a prospective study of 111 children with acute appendicitis, severity of illness correlated well with PCT at admission [13]. Similarly, in 30 children who underwent liver transplantation, PCT elevation on postoperative day 2 was found to indicate poor