

Plasma Fibrinogen and D-dimer in Children With Sepsis: A Single-center Experience

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ABSTRACT

Background & objective: In sepsis, enhanced fibrin formation, impaired fibrin degradation, and intravascular fibrin deposition lead to a prothrombotic state. The current study aimed at measuring various coagulation parameters to predict an early marker for disseminated intravascular coagulation(DIC).

Methods: The current prospective study was conducted from January 2012 to April 2013 on 50 children aged 1-10 years with clinically suspected sepsis referred to the Department of Pediatrics of a tertiary care center in New Delhi, India. Patients were evaluated in accordance with criteria for acute infection (ie, symptoms less than seven days) confirmed in all patients in the laboratory. Patients receiving antibiotics 24-48 hours preceding admission were excluded from the study. Prothrombin time, activated partial thromboplastin time, plasma fibrinogen, and D-dimer were measured at the time of admission in 50 patients and 50 controls.

Results & Conclusion: D-dimer was positive in 36 (72%) patients and negative in all controls. The difference was statistically significant ($P<0.01$). Plasma fibrinogen was significantly ($P<0.01$) higher in patients compared with the controls. It was decreased in 6% and increased in 8% of the patients, and normal in all controls. PT and APTT were significantly ($P<0.01$) higher in patients compared with the controls.

Though none of the current study patients developed overt disseminated intravascular coagulation, the high positivity for D-dimer suggested that it should be measured in children with sepsis for early identification of DIC. This can aid better management as additional coagulation based therapy such as recombinant anti-thrombin and thrombomodulin may help to improve prognosis.

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Introduction

Sepsis is defined as the presence of an infection proven/suspected in a patient with systemic inflammatory response syndrome(SIRS). (1) The manifestations of SIRS include two or more of the following: temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, heart rate $>90/\text{minute}$, respiratory rate $>20/\text{minute}$ along with a total leucocyte count $>12 \times 10^9/\text{L}$ or $>10\%$ immature band forms (2). These are modified in children (1). Sepsis remains the most common cause of death in infants and children worldwide and also in India (2,3). Acute inflammation activates the coagulation system result-

ing in widespread intravascular deposition of fibrin. Impaired fibrinolysis evident by increased levels of plasminogen activator inhibitor-1 further contributes to the presence of fibrin. There is simultaneous depression of natural anticoagulants such as Protein C and Protein S (2). In sepsis, enhanced fibrin formation, impaired fibrin degradation, and intravascular fibrin deposition lead to a prothrombotic state (4). Fibrin (fibrinogen)-degradation products (FDPs) are protein fragments of various sizes that result from the proteolytic action of plasmin on fibrin or fibrinogen. Plasma levels of these fragments are commonly in-

creased in association with disseminated intravascular coagulation (DIC) and fibrinogenolysis, disorders in which their presence is of considerable diagnostic significance (5).

D-dimer, formed on cleavage of cross linked fibrin is a specific marker of fibrinolysis. It is identified in the blood of patients with various thrombotic and thrombolytic disorders (6). It is reported that levels of D-dimer increase in patients with sepsis due to fibrinolysis (7). Other causes of increased D-dimer include venous thromboembolism, syncope, heart failure, trauma, and cancer (8). D-dimer is more specific compared to FDP, which is more sensitive to detect DIC (9).

While activation of coagulation depletes platelets and coagulation factors contributing to clinical bleeding, formation of micro-thrombi causes organ dysfunction (10). DIC remains an independent predictor of organ failure and death in patients with sepsis (11).

Materials and Methods

Subjects

A prospective pilot study was conducted from January 2012 to April 2013 on 50 children aged 1-10 years with clinically suspected acute infection and manifestations of SIRS referred to the Department of Pediatrics of a tertiary care center in New Delhi, India. Patients were evaluated in accordance with criteria for acute infection (ie, symptoms for less than seven days) confirmed in all patients in the laboratory. Patients receiving antibiotics 24-48 hours preceding the admission were excluded from the study. Only 10 patients had a confirmed infection based on blood/cerebrospinal fluid/ pleural fluid culture. Ten patients had radiological evidence of infection (chest X-ray showed features of pneumonia) and in 30 patients infection was diagnosed by elevated proteins (100-500mg/dL) and reduced glucose (<50mg/dL) based on biochemical examination of CSF. Fifty age matched, healthy controls without any clinical evidence of infection were also studied prospectively. Informed consent was taken from the parents/guardians of all children. The study protocol was approved by the Institutional Ethics Committee for human research.

Materials and Methods

Prothrombin time (PT) (Dade Behring Thromborel S), activated partial thromboplastin time (APTT) (Dade Behring Actin FS), plasma fibrinogen (Siemens based on Clauss technique), and D-dimer (Bioscientifica SA, semi-quantitative latex agglutination method) were measured at the time of admission in all patients and controls. All children were followed up for recovery/ DIC/ death for seven days.

Statistical analysis

Unpaired t-test was used to compare blood parameters between the cases and controls. Level of significance was 0.05.

Results & Discussion

The age of the patients (range 1-10 years, mean \pm standard deviation (SD) 6.4 \pm 2.7) and controls (range 1-10 years, mean \pm SD 6.4 \pm 2.7) was not significantly different. Each group comprised of 32 (64%) males and 18 (36%) females. Of the 10 cases positive based on culture (nine on blood culture, one on culture of pleural fluid), *Staphylococcus aureus* and *Klebsiella pneumoniae* were identified in six and four patients, respectively.

PT and APTT were significantly ($P < 0.01$) higher in patients compared with controls. Prolonged PT and APTT were observed in 9 (18%) and 24 (48%) patients, respectively. PT and APTT were normal in all the controls.

Plasma fibrinogen was significantly ($P < 0.01$) higher in patients compared with controls (mean \pm SD of 317.4 \pm 79.5 mg/dL) (reference range: 150-400 mg/dL). The difference was statistically significant. Plasma fibrinogen increased in eight (16%) and decreased in three (6%) patients; and was normal in all controls.

D-dimer was positive in 36 (72%) patients and negative in all controls. The difference was statistically significant ($P < 0.01$). None of the patients had clinical manifestations of DIC such as petechial haemorrhages, purpura or bleeding from any sites.

On follow up for 7 days, five patients died and one had persistent organ dysfunction. The mortality in the

current study was 10%. Three (60%) out of five dead patients had an elevated fibrinogen. D-dimer was positive in all 5 (100%) expired patients.

Sepsis is the systemic inflammatory response to infection. The reported incidence of sepsis in India is 11-24.5/1000 live births (3). Worldwide, it remains the most common cause of death in infants and children (2). Hemostatic abnormalities including DIC and multiple organ dysfunction syndrome are major causes of mortality in such children (4).

In the current study, plasma fibrinogen and D-dimer were estimated in 50 children with sepsis. Plasma fibrinogen increased in eight (16%) and decreased in three(6%) patients. Increase in the level of fibrinogen in patients with sepsis has been observed by other authors (7,12). Fibrinogen is an acute phase reactant and may be elevated in the early stages of sepsis. Kim et al, observed an increased plasma fibrinogen in 43.5% of patients and decreased fibrinogen in 23.5% adult patients with sepsis (13). Lower fibrinogen levels have also been reported in neonates with sepsis (12, 14).The reduced fibrinogen in patients with acute infection may possibly indicate activation of coagulation leading to its consumption.

D-dimer, a specific marker of fibrinolysis was positive in 36 out of 50 (72%) patients. Elevated levels result from activation of coagulation. Kim et al, observed D-dimer positivity in 100% of patients with sepsis (13). Kinasevitz et al, also reported D-dimer positivity in 99.7% of patients with severe sepsis (15). In a study conducted on 47 patients with sepsis, 18 with severe sepsis and 17 with septic shock, D-dimer was detected in 49% of patients and was significantly higher than that of the controls (16). The positivity increased further in severe sepsis and septic shock. Peker et al., studied global fibrinolytic capacity in 61 newborn infants and found that D-dimer levels were significantly ($P<0.05$) higher in patients compared with the controls (17).Hesselvik et al.,studied 53 patients with severe infection; all of them showed positivity for D-dimer but none had overt DIC (7). The mortality in the current study was 10%,while 72% of patients were positive for D-dimer;none of

these patients had clinical manifestations of DIC.The high positivity for D-dimer suggested that it should be measured in children with sepsis for early identification of DIC. This aids better management since additional coagulation based therapy such as recombinant anti-thrombin and thrombomodulin may help to improve prognosis.

Limitations

Patients were followed up for seven days only, hence data beyond this period was not available.

Informed consent

Written informed consent was obtained from the parents/guardians of the patients included in the study.

Conflict of interests

The authors declared no conflict of interest.

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