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Diagnostic utility of biomarkers in diagnosis of early stages of neonatal sepsis in neonatal intensive care unit in Egypt

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KEYWORDS

C-reactive protein;
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Tumor necrosis factor

Abstract *Background:* Neonatal sepsis is considered one of the major causes of morbidity and mortality in NICUs. To avoid unnecessary treatment of non-infected neonates, emergence of multidrug resistance organisms, prolonged hospitalization and a considerable economic burden, particularly in developing countries with poorly-equipped NICUs, an early, sensitive and specific laboratory test would be helpful to guide clinicians in neonatal units to decide whether or not to start antibiotics.

Objective: C-reactive protein (CRP), tumor necrosis factor-α (TNF), interleukin-6 (IL-6) and interleukin-1 (IL-1) were measured in an attempt to identify a set of tests which can confirm or refute the diagnosis of neonatal sepsis at an early stage before administration of antibiotics.

Methods: Assessment of serum levels of CRP, TNF-α, IL-6 and IL-1 was done using quantitative enzyme immunoassay sandwich technique in 116 neonates (36 newborns with clinically suspected sepsis, 48 newborns with culture-proven sepsis and 32 infection-free neonates).

Results: The cutoff levels for CRP at >12 mg/l had a sensitivity of 91% and specificity of 100%, for TNF-α at >113.2 ng/ml had a sensitivity of 83% and specificity of 100%, for IL-6 at >16.8 pg/ml had a sensitivity of 100% and specificity of 47%, and for IL-1 at >15 pg/ml had a sensitivity of 100% and specificity of 47% for the diagnosis of infection before antibiotics.

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Conclusion: The area under ROC curve (AUC) of TNF and CRP in the diagnosis of sepsis was superior to determinations of IL-1 and IL-6. From our data analysis and based on our financial backgrounds, we can conclude that abnormal of CRP levels together with immature-to-total neutrophil ratio above 0.2 with or without elevated IL-1, IL-6 or TNF can be used as early markers of sepsis in neonates.

Introduction

Neonatal sepsis is considered one of the major causes of morbidity and mortality in neonatal intensive care units (NICUs), despite major advances in the management of newborn infants.[1] Blood culture has been considered the gold standard diagnostic test but its analysis takes too long time and lacks sensitivity at early stages.[2] It is also thought that total leukocyte count (TLC), total neutrophil count, immature-to-total neutrophil ratio (I/T), and platelet count also failed to reach the appropriate sensitivity and specificity in this disease.[3]

However, rapid diagnosis is still a major challenge in the management of neonatal sepsis especially at early stages due to non-specific clinical signs that may be minimal and resemble those caused by various non-infective conditions and the fact that infection markers showed difficulty to be interpreted during the early neonatal sepsis.[4–6] Hence it is becoming increasingly important to find an early sensitive and specific biochemical test to differentiate sick newborns with or without infection, especially to minimize the empirical use of antibiotics, emergence of multidrug resistance organisms, prolonged hospitalization and a considerable economic burden, particularly in developing countries with poorly-equipped NICUs like Egypt.[7,8]

Finding a reliable laboratory test as a marker for immediate detection of infection with acceptable sensitivity and specificity has always been controversial among investigators. Recently various biochemical markers, for example C-reactive protein (CRP), tumor necrosis factor (TNF-α) and interleukins have been evaluated as potential indicators for early identification of septic infants.[7]

The aim of this study was to evaluate CRP, TNF-α, interleukin-6 (IL-6) and interleukin-1 (IL-1) as potential early diagnostic markers of neonatal infection. We also aimed to determine the specificity and sensitivity of interleukins in early detection of neonatal infection, and suggest cutoff values for studied interleukins in order to detect infections.

Subjects and methods

Subjects

All neonates admitted to the NICU of Cairo University during the period from June 2014 to December 2014, were enrolled in this study. Of 181 eligible infants, 116 were enrolled in the study; 65 infants were excluded because insufficient blood sampling, incomplete documentation, history of perinatal asphyxia, inter-current illnesses, known congenital anomalies, chromosomal abnormalities or inborn errors of metabolism, confirmed intrauterine viral infection and who were already receiving parenteral antibiotic at the time of study.

The study protocol was approved by the Ethical Committee of Cairo University & the Ethical Committee of National Research Center, Cairo, Egypt. A written consent was obtained from parents of neonates included in the study.

Full medical history was obtained from the parents then all neonates are subjected to full clinical examination, especially for the clinical signs of infections (poor peripheral perfusion, capillary refilling time >3 s, hypotension, hypothermia or hyperthermia, poor neonatal reflexes, hypotonia, abdominal distension, tachypnea, increased or decreased heart rate). Routine complete blood count, differential TLC, blood cultures and other relevant cultures were done for all patients at the time of enrollment.

According to results of previous parameters, neonates enrolled in the study were divided into three groups:

1- Culture-proven sepsis group where sepsis was confirmed by a positive blood culture or other relevant cultures accompanied by compatible signs and symptoms.
2- Clinically suspected sepsis group that was defined as clinical symptoms and/or signs suggestive of sepsis and necessitated the start of antibiotic therapy but not confirmed by laboratory tests (negative culture).
3- Control group that includes all infection-free neonates, without clinical findings or maternal risk factors for infection, admitted for minor problems or nursed in the neonatal ward at the same period.

Methods

Adequate venous blood samples were taken from each infant for analysis in the first 6 h of admission and before administration of antibiotics. Blood samples were collected into plain evacuated blood tubes and were allowed to clot for 60 min then centrifuged at 4000 rpm for 10 min. Hemolyzed samples were excluded from analysis. After separation, routine analysis and assessment of CRP were done and aliquots of serum were frozen at -80 °C for TNF-α, IL-6 and IL-1 analysis.

CRP, TNF-α, IL-6 and IL-1 were assessed using Quantikine ELISA kit, R&D, Bio-Techne, Minneapolis, USA.[3]

Statistical analysis

Statistical calculations were done using Statistical Package for the Social Science (SPSS Inc., Chicago, IL, USA) version 16 for Microsoft Windows. Data were statistically presented in terms of mean, standard deviation (SD), and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using one way analysis of variance (ANOVA) test. For comparing categorical data, Chi square test was performed. Exact test was used instead when the expected