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NEUTROPHILS CD11B EXPRESSION AS BIOMARKER IN THE EARLY DIAGNOSIS OF NEONATAL SEPSIS.

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ABSTRACT:

Objective: we aimed to assess the value of neutrophils CD11b for the early diagnosis of neonatal infection and its relation with other laboratory marker as hematological and CRP.

Design: the study was conducted among newborns hospitalized for " rule out of sepsis" to neonatal intensive care unit (NICU) .

1-Subjects and setting: a total of 90 newborns [30 neonates with proven sepsis clinically and positive blood culture (patients group),30 clinical symptoms of sepsis and negative blood culture and may negative CRP(suspected group) and 30 healthy newborns(control group)] were enrolled in the study. On admission to NICU ,blood was sampled for CRP, complete blood count (CBC), blood culture and CD11b marker before starting antibiotic therapy .

Results In this study, at a cut off level of CD11b was 17.8, the sensitivity was 98.33%,the specificity was 100%, positive predictive value (PPV) was 100% and negative predictive value (NPV) was 96.77%. And CRP, the sensitivity was 76.7%, the specificity was 100%, positive predictive value (PPV) was 100% and negative predictive value (NPV) was 68.2%.CD11b was elevated in patients group compared to the control group.

Conclusion: Measurement of CD11b as a marker on surface of blood neutrophils can be useful for diagnosis of neonatal sepsis in the early phase.

INTRODUCTION:

Neonatal sepsis is a major cause of morbidity and mortality. Early diagnosis and treatment of the neonate with suspected sepsis are essential to prevent life-threatening complications **(6).**Diagnosis and management of sepsis are a great challenge facing neonatologists in Neonatal intensive care units. Early warning signs and symptoms are often protean and non-specific. Then there is the difficulty of distinguishing the clinical picture of neonatal sepsis from non-infectious causes. **(*5*).**Unfortunately there is no single diagnostic test, which can reliably diagnose sepsis in the newborn, therefore many diagnostic tests are utilized to diagnose or confirm sepsis. Several hematological tests were used for the early and reliable diagnosis of neonatal sepsis in the early and mid 1980's. The non-specific nature of these tests has directed investigators towards finding more specific and earlier increasing infection markers **(*10*).**Because of the advances in flowcytometric technology, this study paid attention to CD11b, a neutrophil surface antigen, and its sensitivity and specificity in diagnosis of neonatal sepsis. CD11b is a cell surface antigen of neutrophil and is normally expressed at a very low level on the surface of non-activated cells. Its expression on neutrophil cell surface, however, increases substantially within a few minutes after the cell comes into contact with bacteria or endotoxins ***(1).***

METHODS:

This study was conducted on 90 neonates, 30 neonates with proven sepsis clinically and positive blood culture (patients group),30 clinical symptoms of sepsis and negative blood culture and may negative CRP(suspected group) admitted to Neonatal Intensive Care unit In addition, and 30 healthy newborns(control group) of comparable age and sex taken randomly from the follow up clinic. a congenital abnormality, congenital infection, hypoxic ischemic enchephalopsy, birth injury &metabolic disorder were considered as exclusion criteria.

All the study population were subjected to the following:

1. History taking.
2. Clinical examination.
3. Laboratory Investigations including: Complete blood count.

Blood cultures for isolation of the causative organism and its identification.

Measurement of CRP.
Measurement of CD11 by flowcytometry

Statistical analysis

The statistical analysis was conducted using STATA/SE version 11.2 for Windows (STATA corporation, College Station, Texas).

Data were analysed by sensitivity and specificity derived from the receiver operating characteristic (ROC) curve . A p value of <0.05 was considered significant.

RESULTS

Respiratory distress ,Lethargy ,poor reflexes, poor feeding and were the commonest presentation of sepsis in our study followed by cyanosis, vomiting, shock, temperature instability, seizures and hypoglycemia manifestations were the least presentation of sepsis.

Our study reveals highly significant decrease in Hct%, Hb, TLC in the patients group when compared with that of the control.

On the other hand, there were highly significant increase in I/Tratio ,I/M ratio and HSS in patients group when compared with that of the controls.

Results of blood cultures in the septic neonates showed that Gram-negative Klebsiella was the most frequently isolated organism (40%) followed by Staph aureus (36.6%) ,E. Coli (10%), Candidiasis (6.6%), Pseudomonas (3.3%) and serratia (3.3%).

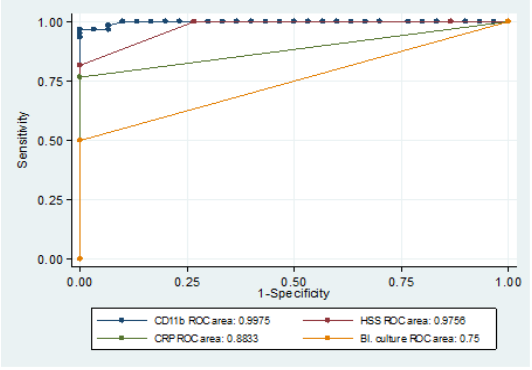
In this study, at a cut off level of CD11b >76.7 the sensitivity was 80%, the specificity was 100%, positive predictive value (PPV) was 100% and negative predictive value (NPV) was 76.9%. And CRP, the sensitivity was 76.7%, the specificity was 100%, positive predictive value (PPV) was 100% and negative predictive value (NPV) was74.1%.

Cd11b was elevated in septic neonates compared to the control group.

ROC analysis for the prediction of neonatal infection

	CD11b	CRP	HSS	Blood culture
Cutoff	17.8	-	3	-
Sensitivity (%)	98.33	76.7	81.67	50.0
Specificity (%)	100.0	100.0	100.0	100.0
PPV (%)	100.0	100.0	100.0	100.0
NPV (%)	96.77	68.2	73.2	50.0
Correctly classified (%)	98.89	84.44	87.78	66.67
AUC	0.9989	0.883	0.9756	0.75
P	<0.001 (HS)			

Cd11b was positive with higher sensitivity 98.3%,than CRP & HSS &blood culture as there sensitivity was (76.7% ,81.6%,50%) respectively.



DISCUSSION

Neonatal sepsis remains a major cause of mortality and morbidity in the newborn. This is despite the advances in perinatal and neonatal care and use of very potent antibiotics. However, early recognition and intervention clearly improves the outcome for neonates with infections**(14).**The World Health Organization (WHO) estimates that more t h a n one million neonatal deaths around the world each year are caused by severe infections, and around one million deaths are due to neonatal sepsis or pneumonia alone **(13).**Incidence of neonatal sepsis varies from 1 to 5 cases per 1000 live birth in developed countries, but gets higher in developing countries which varies from 49 to 170 per 1000 ***(15)***. Regarding CRP, our study revealed a significant increase in CRP in septic group compared to suspected group. The same results obtained by ***Cekmez et al., (2011)*** where CRP had increased in highly probable sepsis, in comparison to possible sepsis, & in probable sepsis, compared to possible sepsis.C-reactive protein is synthesized in the liver in response to inflammatory cytokines and may increase more than 1000 folds during an acute phase response **(8).** It is released 4 to 6 hours after the onset of a stimulus, reaches a peak at 24 to 48 hours and then diminishes as the inflammation resolves ***(5).***Because of its short half-life (4-6 hours), CRP level can be expected to fall quickly after efficient elimination of the microbial stimulus **(4).** The use of CRP to exclude infection may allow clinicians to discontinue antibiotics at 48 hours in selected infants, limiting unnecessary antibiotic exposure **(7).**

In the present study the sensitivity of blood cultures in neonatal sepsis is low and this may explained by the number and timing of cultures taken, blood volume, culture medium, technique, temperature and organism density **(9).** Recent studies have shown that increased level of CD11b on surface of blood neutrophils occurs during the initial phase of neonatal septicemia. It has been suggested that this marker have high sensitivity and specificity, and thus, may serve as useful diagnostic marker for early detection of neonatal sepsis. CD11b is a cell surface antigen of neutrophi & is normally expressed at a very low level on the surface of non-activated cells, its expression on neutrophil cell surface increase within a few minutes after the cell comes into contact with bacteria or endotoxins **(11).** In the current study we found that level of CD11b on surface of neutrophils was significantly high in cases group indicating that the level of CD11b is a good marker for the diagnosis of neonatal sepsis.***Weirich et al.,(1998) and Nupponen et al.,(2001)*** revealed that expression of CD11b was much higher in neonate of sepsis than control group .But, ***Cui et al. (2003)*** have shown that expression of CD11b was lower in neonates with sepsis than control group.Finally we concluded that rapid accurate diagnosis of neonatal sepsis is still a major challenge for workers in the field of neonatal care. The results of present study and previous studies showed that the measurement of neutrophil surface markers can be useful for diagnosis of infection in the early phases. Also, the quantitative measurement of CRP in addition to CD11b further enhances the ability to diagnose infections and improves sensitivity and negative predictive value to 100%.

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