Diagnostic Value of C - Reactive Protein and Other Hematological Parameters in Neonatal Sepsis

Hafadh Jaleel Hussein*, Yusra Fayyadh Alwan**

ABSTRACT:

BACKGROUND:

There have been many attempts to develop screening tests or scoring systems that can identify infected infants at the time of initial assessment, sparing others from invasive diagnostic procedures, intravenous antibiotics therapy, mother-infant separation and parental anxiety.

OBJECTIVE:

Is to analyze hematological parameters and C - reactive protein so as to evaluate their diagnostic value in neonatal sepsis.

PATIENTS AND METHODS:

A cross-sectional study was performed in the neonatal care unit (N.C.U) at the Central Teaching Hospital for Pediatrics and Al-Habibiya Maternity and Children Teaching Hospital during a period from the first of June 2005 to the first of January2006

One hundred neonates having clinical features of sepsis and 100 normal asymptomatic neonates were evaluated with a set of investigations including C-reactive protein(CRP), White Blood Count(WBC), Absolute Neutrophil count (ANC), Platelets count (thrombocytopenia), Immature to Total neutrophil ratio (I/T ratio) and Erythrocyte Sedimentation Rate (ESR) to diagnose neonatal sepsis.

RESULTS:

C-reactive protein (CRP) was positive in (82.4%) of group-A and (81.8%) of group-B and had a specificity of 93.0%. ANC was the second most sensitive test having sensitivity of 61.8% for group-A and 48.5% for group-B and specificity of 86.0%.

The sensitivities of platelets count (thrombocytopenia), WBC, I/T ratio and ESR for group-A were: 55.9%, 29.4%, 17.6% and 26.5% respectively, with specificities of 91.0%,
89.0%, 92.0% and 81.0% respectively. While group-B had sensitivities of 42.0%, 33.3%, 15.2% and 22.7% respectively with specificities of 91.0%, 89.0%, 92.0% and 81.0%respective ly.

CONCLUSION:

The implementation of CRP and other hematological parameters (ANC, Platelets count and WBCs) are useful in early detection of neonatal sepsis and diagnosis of neonatal sepsis in those who have false negative blood cultures.

***KEY WORDS*:** neonatal sepsis, C- reactive protein, hematological parameters.

INTRODUCTION:

The early recognition and diagnosis of neonatal sepsis is difficult because of the variable and non-specific clinical presentations of this condition. It is extremely important to make an early diagnosis of sepsis because prompt institution of antimicrobial therapy will improve outcome [(1)]. In an effort to do so, the empiric use of antibiotics has increased, creating an environment for emerging bacterial resistance .Isolation of bacteria from blood, cerebrospinal fluid (CSF) and urine culture may take up to 72 hours before being considered negative, thus even infant with no sepsis usually receive at least three days of antibiotic therapy[(2)].

*Ibn AL-Baladi Obstetrics and Pediatrics Hospital.

**AL Khalis General Hospital .

PATIENTS AND METHODS:

The studied subjects included 100 neonates admitted to the N.C.U with a clinical diagnosis of Neonatal Sepsis (N.S.), having either non-

specific signs and symptoms or focal signs of infection and 100 healthy neonates were chosen randomly from
the postnatal ward of the obstetrics department at
Al-Habibiya Maternity and Pediatrics Teaching Hospital. The remaining of healthy neonates were collected from department of vaccination at Central Teaching Hospital for Pediatrics.Neonates
who had congenital malformations, birth asphyxia, inborn error of metabolism, hemolytic jaundice, gestational age < 33 weeks, respiratory distress syndrome (due to surfactant deficiency) , those who received antibiotics prior to admission and those with birth weight < 2.0 kg were excluded (keeping in mind that low birth weight infants are those weighting < 2.5 kg at birth). A written consent of the parents for both studied groups was obtained for inclusion of their neonates in the study. All patients underwent a detailed history, complete physical examination and relevant hematological, microbiological and radiological examination to explore all possible sources of infection.Every patient was administered intravenous antibiotics that were a combination of Ampicillin and third generation cephalosporin (Cefotaxime).Positive blood culture was taken as the gold standard for the diagnosis of neonatal sepsis, whereas, other hematological tests were performed on all (200 babies) including both sick and healthy neonates. For analysis of the results, the neonates were divided into three groups; the confirmed cases of neonatal sepsis with positive blood culture were labeled as group-A, symptomatic neonates having clinical diagnosis of sepsis but negative blood culture were labeled as group-B and normal asymptomatic neonates, who served as control, were labeled as group-C.The samples (3ml.) of blood were collected for complete blood count (C.B.C.) including platelets count and Erythrocyte Sedimentation Rate (ESR).
Absolute Neutrophil Count (ANC) and immature neutrophils count were performed manually on Leishman stained blood smear.Under strict aseptic measures samples of blood (2ml.) for culture and sensitivity were collected, these 2ml. of blood were added to a bottle containing (18ml.) Brain-Heart infusion broth. One ml. of blood was collected in a tube without EDTA and was used for estimation of C-reactive protein (CRP) by latex agglutination technique. The cut off values of the studied parameters for positive tests were:C-reactive protein (CRP) > 6mg./l, Erythrocyte Sedimentation Rate (ESR) > 15mm/hr. , Platelets count < 150000/cmm., White Blood cells Count (WBCs) < 5000/cmm. Or >20000/cmm., Absolute Neutrophil Count (ANC)-an age adjusted normal reference range was used and neutrophilia and neutropenia were considered abnormal, Immature to Total neutrophils ratio (I /T) ratio > 0.2 considered abnormal(3) .Data were analyzed by SPSS programme for windows. The sensitivity, specificity, positive predictive value (PPV) and negative predictive (NPP) value for each test in group A and B were calculated.**RESULTS:**In group –A, CRP has the highest sensitivity (82.4%), specificity (93.0%), PPV (80.0%) and NPV (93.9%) followed by ANC with sensitivity of (61.8%), specificity (86.0%), PPV(60.0%) and NPV (86.9%) then platelets count with sensitivity of (55.9%), specificity (91.0%), PPV (67.9%) and NPV (85.8%) followed by WBCs with sensitivity of (29.4%), specificity (89.0%), PPV (47.6%) and NPV (78.8%) while ESR and I/T ratio were the lowest; with sensitivity (26.5%,17.6%), specificity (81.0%,92.0%), PPV(32.1%,42.9%) and NPV (76.4%,76.7%) respectively. As in table 1

Table 1: Sensitivity, specificity, PPV and NPV of hematological parameters and CRP in group-A (proven sepsis)

test		Proven sepsis n=34	healthy	Sensitivity	specificity	FN%	FP%	PPV	NPV
CRP	POS	28	7	82.4	93.0	17.6	7.0	80.0	93.9
	NEG	6	93						
ANC	POS	21	14	61.8	86.0	38.2	14.0	60.0	86.9
	NEG	13	86						
PLATELETS < 150000/cmm	POS	19	9	55.9	91.0	44.1	9.0	67.9	85.8
	NEG	15	91						
WBC	POS	10	11	29.4	89.0	70.6	11.0	47.6	78.8
	NEG	24	89						
ESR >15 mm/ hr	POS	9	19	26.5	81.0	73.5	19.0	32.1	76.4
	NEG	25	81						
I / T	POS	6	8	17.6	92.0	82.4	8.0	42.9	76.7
	NEG	28	92						

In group – B, CRP has the highest sensitivity (81.8%), specificity (93.0%), PPV (88.5%) and NPV(88.6%) followed by ANC with sensitivity of (48.5%), specificity(86.0%), PPV(69.6%) and NPV(71.7%) then platelets count with sensitivity of (42.4%), specificity(91.0%), PPV (75.7%) and NPV(70.5%) followed by WBCs with sensitivity of (33.3%), specificity (89.9%), PPV (66.7%) and NPV (66.9%). While ESR and I/T ratio were the lowest with sensitivity of (22.7%, 15.2%), specificity (81.0%, 92.0%) PPV (44.1%, 55.6%) and NPV (61.4%, 62.2%). As in table 2

Table 2: Sensitivity, specificity, PPV and NPV of hematological parameters and CRP in group-B (probable sepsis)

test		Probable sepsis	healthy	Sensitivity	specificity	FN%	FP%	PPV	NPV
CRP	POS	54	7	81.8	93.0	18.2	7.0	88.5	88.6
	NEG	12	93						
ANC	POS	32	14	48.5	86.0	51.5	14.0	69.6	71.7
	NEG	34	86						
PLATELETS < 150000/cmm	POS	28	9	42.4	91.0	57.6	9.0	75.7	70.5
	NEG	38	91						
WBC	POS	22	11	33.3	89.0	66.7	11.0	66.7	66.9
	NEG	44	89						
ESR >15 mm/ hr	POS	15	19	22.7	81.0	77.3	19.0	44.1	61.4
	NEG	51	81						
I / T	POS	10	8	15.2	92.0	84.8	8.0	55.6	62.2
	NEG	56	92						

POS = positive, NEG = negative, FN = false negative, FP = false positive

DISCUSSION:

A test of high sensitivity and high negative predictive value should ideally detect all infected cases so that the disease can be easily excluded [(4)].

In the present study, (34%) of cases that were clinically suspected to have sepsis had a positive blood culture. While Tariq Ghafoor et al, 2005 has reported that(28%) of cases of NS had positive blood culture [(5)]. However, Anwar et al, 2000 has documented (42%) blood culture positive cases of NS[(6).] Also Aurangzeb et al, 2003, has reported (55.8%) culture positive N.S[(7)]. This variation in blood culture positively may depend on the criteria of studied group, volume sample and sampling site.

Although it is not specific for neonatal sepsis, CRP has the highest sensitivity, specificity and high NPV and PPV [(6)].

In this study, the results have shown that the sensitivity, specificity, PPV and NPV of CRP were: 82.4%, 93.0%, 80.0% and 93.9% respectively for proven sepsis (group-A) and 81.8%,93.0%, 88.8% and 88.6% respectively for probable sepsis (group-B). These results are similar to that of Tariq Ghafoor et al, 2005, who observed that the sensitivity, specificity, PPV and NPV of CRP were: 85.5%, 95.0%, 82.7% and 95.9% respectively for proven sepsis, and 80.5%, 95.0%, 92.1% and 87.1% respectively for probable sepsis [(5)]. Shabbir et al, 1994, found that CRP had 74.0% sensitivity and 76.0% NPV [(7)].

The sensitivity and specificity of CRP were more or less similar in both proven and probable cases of sepsis but the NPV and PPV were different between the two groups. The discrepancy in sensitivity, specificity, NPV and PPV in different studies may be due to different methods of CRP estimation and/or variation in criteria of positivity of the test.

This study documented a relatively lower sensitivity for A.N.C., Platelets and WBCs which were as follow: 61.8%, 55.9% and 29.4% respectively for proven sepsis(group-A) and 48.5%,42.4% and 33.3% for probable sepsis (group-B) respectively, but still they have high specificity (86.0% , 91.0% and 89.0%) for group-A and Brespectively. In this study, nevertheless, A.N.C. was the second most sensitive test in detection of N.S after CRP. Tariq Ghafoor et al, 2005, has reported ANC, Platelets

and WBCs with sensitivity of 71.4%, 64.3%and 39.3% respectively for proven sepsis and 63.9%, 40.3% and 27.8% respectively for probable sepsis with specificity of 61.0% , 99.0% and 92.0% respectively [9].

Nevertheless, thrombocytopenia had moderate sensitivity (55.9%) for group-A and (42.4%) for group-B in our study, however it has high specificity (91.0%). The discrepancy in sensitivity of these parameters may be due to severity of infection, age of the neonate or criteria of studied group; as thrombocytopenia is generally observed late in the neonatal sepsis and they were normal when the neonatal sepsis has been diagnosed and neutropenia is also observed in conditions other than neonatal sepsis like infants whose mothers had hypertension or in neonates with severe perinatal asphyxia and intraventricular or periventricular hemorrhage.

Although we tried as much as possible to exclude neonates with birth asphyxia but we did not exclude those with maternal hypertension.

In this study, ESR had the lowest sensitivity and NPV (26.5%, 76.4%) and (22.7%, 61.4%) for group-A and group-B respectively that makes ESR a poor predictor of sepsis. This observation is in agreement with the finding of Shabbir et al,1994, who observed that ESR had a sensitivity of (19.0%) and NPV of (56.0%) (8). Contrary to this, Misra et al, 1989, found that ESR had a high sensitivity (90.0%) [10].

This variation is due to the fact that at least four hours are required for hematological response to develop after onset of infection and blood samples collected earlier than 4 hours will give normal results [11, 12].

It's important to say that it was difficult to obtain 2 blood samples with a period in between because many parents refused that; also it was too much for the laboratory staff to do.

We found that I/T ratio had very low sensitivity and NPV (17.6%, 76.7%) respectively for group-A and (15.2%, 62.2%) respectively for group-B.

This finding is in agreement with the finding of Tariq Ghafoor et al, 2005, who observed that I/T ratio had a sensitivity of (25.0%) and (20.8%) for both proven and probable sepsis respectively [5].

Contrary to that, a study from Switzerland reported good sensitivity of I/T ratio (78.0%) and (73.0%) for proven and probable sepsis respectively [13]. Likewise, Misra et al, 1989, found that I/T ratio was the most sensitive index for N.S [10].

This discrepancy in sensitivity of I/T ratio may be due to different cut off values used, as some studies consider I/T ratio ≥0.2 is significant while others consider it ≥ 0.3 or > 0.15. However, in our study we have considered that I/T ratio of ≥ 0.2 is significant for sepsis.

CONCLUSION:

CRP has the highest sensitivity, specificity, PPV andNPV in both culture positive and culture negative neonatal sepsis.

Absolute Neutrophils Count (ANC) is the second most sensitive test in detection of neonatal sepsis followed by platelets count and WBCs.

ESR and I/T ratio have the lowest sensitivity, specificity, NPV and PPV in both culture positive and culture negative neonatal sepsis.

This set of investigations (CRP, ANC, Platelets count and WBC) are useful in early diagnosis of neonatal sepsis i.e. before the appearance of blood culture results. Also they guide us so as not to miss any case of sepsis even if the blood culture result was a false negative one.

Recommendations:

We recommend using this set of investigations as they are readily available, inexpensive and sensitive in detection of neonatal sepsis, sparing others from invasive diagnostic procedures like lumbar puncture that was done unnecessarily and to avoid prolonged mother-infant separation and parental anxiety.

Further studies are required to validate our results.

Further studies may be required to show the benefit of this set of investigations for follow up of neonates with sepsis; as when to stop antibiotic therapy in cases of neonatal sepsis?

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