ROLE OF C-REACTIVE PROTEIN IN DIAGNOSING NEONATAL SEPSIS

Anwar Zeb Jan[1], Shahzada Bakhtyar Zahid[1], Samreen Ahmad[1]

ABSTRACT

Objective: *To determine the sensitivity and specificity of C-reactive protein (CRP) in diagnosing neonatal sepsis.*

Methodology: *A cross sectional study of neonates suspected to have sepsis was carried out in the neonatology department of Rehman Medical Institute Peshawar Pakistan. The duration of study was from 1stJan, 2010 to 31st Dec, 2011. A total of 300 cases were selected who were fulfilling the criteria for neonatal sepsis. C-reactive protein and blood cultures were done in all cases following a standard protocol.*

Results: *Among 300 neonates selected, sepsis was confirmed among 56 % (167 of 300) cases. This was done on the basis of positive blood culture. In 66% (198 of 300) cases C-reactive protein was positive with the Sensitivity, specificity, negative and positive predictive values of 94.01%, 69.17%, 79.29%, 90.19% respectively. The diagnostic accuracy of CRP was 83.0%.*

Conclusion: *C-reactive protein is a good diagnostic test index and can identify the infection in neonates at the time of initial assessment.*

Key Words: *Neonatal Sepsis, C-Reactive Proteins, Blood Cultures*

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INTRODUCTION

Sepsis is one of the major problems in neonates. Out of the 5 million neonatal deaths per annum, 30-40% of deaths are due to infections.[1] Incidence of neonatal sepsis in developed countries is 1-4/1000 live births.[2] In Pakistan the data regarding sepsis is limited but is thought to be roughly three times more than that of developed countries.[3] In Bangladesh neonatal mortality rate is 42/1000 live birth.[4]

The neonatal sepsis at time is very difficult to diagnose on clinical criteria alone because of its non-specific and variable sign and symptoms.[5] The clinical signs of neonatal sepsis are often non-specific; empiric antibiotic therapy may result in the treatment of as many as 30 uninfected neonates for everyone who is eventually diagnosed to be infected.[6-8]

The use of safe and effective antimicrobial therapy has markedly reduced the neonatal mortality.[9] Though empirical therapy with antibiotics seems reasonable given the dire outcome of missed diagnosis but improvement in diagnostic accuracy should diminish the exposure of healthy neonates to the risk of un-wanted antimicrobial therapy, psychological stress of prolong stay and financial overburden.

On contrary, under treatment is also dangerous and at time can lead to serious mortality and morbidity. In this dilemma, a very narrow line for neonatologist is to treat or not to treat. We as a neonatologist need a laboratory test that is easily available, cost effective and results are readily available. So C-reactive protein is set as a screening test, though blood culture is a gold standard but waiting for the results for such long can lead to serious complications. The difficult technique of blood culture collection under proper sterilize and hygienic condition, delayed and spurious results.

The C-reactive protein was first introduced in 1930 by tellips and Francis, the C-reactive protein was set as a screening device for inflammation, a marker for disease activity and as a diagnostic adjunct.[10] C-reactive protein is an inflammatory marker that is synthesized in the liver in response to inflammatory cytokines and plays a major role in innate immunity. The level of C-reactive protein rises rapidly with a peak level in 6 hours, even up to thousands folds during an acute response. It has a short half-life of 19 hours, so the level falls rapidly once the source is removed.[9,11]

CRP is a useful infective marker as compared to leukocyte counts in the neonates, which varies significantly

1: Department of Pediatrics, Rehman Medical Institute Peshawar, Pakistan

Address for correspondence:

Anwar Zeb Jan
Consultant Department of Pediatrics,
Rehman medical institute Peshawar, Pakistan
Tel # 0092-91-5825501-8
Fax #: 0092-91-5810055
Email: fanwar10@gmail.com

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in the early neonatal period and hence cannot be set as a diagnostic test for confirmation of sepsis. In a recent comprehensive systemic review of the literature evaluating leukocyte ratios and C-reactive protein, there is wide range of sensitivity and specificity for leukocyte count and ratios, similarly C-reactive protein measurement showed variable accuracy though better than leukocyte count. Though blood culture is a gold standard test but due to some pit fall we need a test that is readily available, cost effective and less time consuming. We consider C-reactive protein as an indicator of neonatal sepsis, at the same time we cannot consider C-reactive protein as a sole indicator but may be regarded as a step in approach to work up and in combination of other tests like blood culture, also with C-reactive protein we can determine the severity of neonatal sepsis while waiting for blood culture results that may even be negative in some fatal infections.[12]

This study was planned to determine the sensitivity and specificity of C-reactive protein in diagnosing neonatal sepsis in our set up.

METHODOLOGY

The study was conducted at neonatology unit of Rehman Medical Institute Peshawar, over a period of 2 years from 1st January 2010 to 31st December 2011. Rehman Medical Institute is a tertiary care hospital with grade IIIA care NICU.

Out of 1200 patient admitted to the neonatology unit, 300 cases were conveniently selected with clinical signs or symptoms of sepsis like fever, lethargy, poor feeding, jaundice, hypothermia, poor perfusion, diarrhoea, vomiting, abdominal distension, prolong capillary refill, weak or excessive cry, grunting, apnea, bulging anterior fontanel or any maternal risk factor like maternal pyrexia (within first week of prenatal and 48 hours of postnatal, foul smelling vaginal discharge, premature rupture of membranes (PROM) 18hours, maternal UTI in last month, instrumental delivery. All the neonates were examined in detail by the pediatric trainees in NICU. The data was recorded on a data sheet. Each neonate was carefully examined according to the criteria screened for sepsis.

Neonates with birth asphyxia, meconium stained liquor, low birth weight (< 1500 grams), preterm babies (<32 weeks) or neonates who were already on antibiotics therapy were not included in the study.

Blood for blood culture and C-reactive protein was taken under strict aseptic condition. Samples were sent to pathology department in aseptic and controlled environment. The blood was followed for 7 days for blood cultures and a confirm report was taken. A standard procedure was followed for both CRP and Blood culture.

CRP:

For any patient with suspected neonatal sepsis a CRP test was done. In our setup we perform a quantitative test. After sterilization of the skin 1-2ml of blood was put in a bottle tube (with no anti-coagulant), then the blood was centrifuged for 5 minutes, the serum was separated using a suitable pipette, drop 5ul of sample on control beside each drop of latex. Rotate the slide in machine for some time, the results will be displayed on the computer screen a value of greater than 0.5mg/dl is consider as positive in our setup. The test is purely quantitative.

BLOOD CULTURE:

The blood was collected under strictly hygienic condition to avoid contamination. The staff involved in the procedure wore sterile glove and were properly scrubbed. The blood was then drawn from a vein after sterilization of the skin thoroughly with sterile spirit swab; 1-3ml of blood was drawn and put in a blood culture bottle (BD BACTEC Peds plus/F culture vials) which contains40ml of culture media. The culture media bottle is kept at 37 C in BACTEC machine, which automatically detect growth of organisms. Upon detection the machine give bleep. The culture media is then taken out of the machine and put on a culture media plates (Blood, Chocolate and Mecconci media are used). When there is significant growth then this growth is subjected to sensitivity.

RESULTS

During the study period, 300 neonates were included based on selection criteria; these comprised 205 (68.3%) males and 95 (31.7%) females with ages ranging from 1 day to 28 days. Their demographic data are displayed in Table 1.

Table 2 provides data of laboratory investigations of neonates (Blood culture and CRP levels).

Mean values are shown in table III. There were no significant differences among genders.

Using a 2 x 2 table, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall accuracy of CRP levels were calculated as shown in table IV.

Sensitivity obtained was 94.01%, Specificity 69.17%, PPV 79.29%, NPV 90.19% and overall accuracy 83.0%.

DEMOGRAPHIC DATA OF NEONATES

Age (days)	Male (n=205)		Female (n=95)		Total (n=300)	
	No.	%	No.	%	No.	%
1 - 7	80	39.0	36	37.9	116	38.7
8 – 14	39	19.0	29	30.6	68	22.7
15 – 21	57	27.9	16	16.8	73	24.3
21 – 28	29	14.1	14	14.7	43	14.3

Table I

LABORATORY INVESTIGATIONS OF NEONATES

Variables	Male (n=205)		Female (n=95)		Total (n=300)	
	No.	%	No.	%	No.	%
Blood culture						
Positive	111	54.1	56	58.9	167	55.7
Negative	94	45.9	39	41.1	133	44.3
CRP levels						
Normal	65	31.7	37	38.9	102	34.0
High	140	68.3	58	61.1	198	66.0

Table II

MEAN VALUES OF AGE AND CRP LEVELS AMONG MALE AND FEMALE PATIENTS

Variables	Male (n=205)	Female (n=95)	Overall (n=300)
	Mean ± S.D	Mean ± S.D	Mean ± S.D
Age (days)	11.92 ± 8.15	11.41 ± 8.10	11.76 ± 8.12
CRP levels (mg/dl)	3.05 ± 4.21	3.73 ± 4.80	3.27 ± 4.40
CRP normal	0.22 ± 0.15	0.22 ± 0.16	0.22 ± 0.15
CRP high	4.37 ± 4.53	5.96 ± 4.99	4.83 ± 4.71

Table III

COMPARISON OF BLOOD CULTURE AND CRP

		Blood culture		Totals
		Positive	Negative	
CRP	**High**	157	41	198
	Low	10	92	102
Totals		167	133	300

Table IV

DISCUSSION

Neonatal sepsis is a serious and potentially life threatening condition. Early diagnosis of neonatal sepsis is very difficult and essential for reducing the mortality and morbidity in neonates. No doubt blood culture is still the gold standard but because of its non-availability in most peripheral setups, high cost, more chances of contamination and delayed results, a need more convenient, cost effective and whose results are available in time.

C-reactive protein has some practical advantages: it can be done in all those neonates who are on prior antimicrobial therapy.[13] Despite all this still it is recommended to rely on both clinical correlations and laboratory findings for confirm diagnosis.

In this study 56 % (168 of 300) neonates were proved to have neonatal sepsis which was based on positive blood culture. Other studies showed a proved sepsis ranging from 20-30 % (Pavenik-Arnol et al., 2004; Naher et al., 2011Abdollahi et al., 2012).[14-16]

This study showed that C-reactive protein was positive in 66 % (198 of 300) of neonates. 79% (157 of 198) neonates were having confirmed sepsis. C-reactive protein was best single marker with an overall sensitivity and specificity of 94.01% & 69.17%. Our results are comparable with the study done by William E, Benitz et al, which was done in Stanford, California that shows C-reactive protein had higher sensitivity 92.9% and 85% for proven and probable sepsis and 78.9% and 84.4% for proven sepsis in early and late onset episodes.[17]

As compared to the studies done by Boraey NF, et al[18], our result have a NPV (89%) of and comparatively low PPV (79%).

The marked difference of result among studies evaluating C-reactive protein as useful marker can be explained by non-availability of universally acceptable definition of neonatal sepsis, difference in reference range values and environmental influence on the results in different setups.

We used quantitative technique for C-reactive protein determination. This is easy to perform and results are available in an hour time. Furthermore it can also be used effectively in neonates who had already used antibiotics.

CONCLUSION

Al-though blood culture is still a gold standard test in diagnosing sepsis but its main drawback is its delayed result, more chances of contamination, high cost and non-availability in most peripheral setups in our country. This has prompted evaluation of surrogate markers of inflammation as possible tool for diagnosis of bacterial sepsis. Our study suggests that CRP should be used as a preferred marker in evaluating a neonate for sepsis. Despite the high sensitivity C-reactive protein we would still stress upon clinical correlation and laboratory findings should be used simultaneously for the diagnosis of neonatal sepsis.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under

AZJ: Conception and design, drafting the manuscript, supervision, final approval of the version to be published

SBZ: Data analysis, Critical Revision and Final approval of the version to be published

SA: Acquisition of data, Final approval of the version to be published

CONFLICT OF INTEREST

Authors declare no conflict of interest

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KMUJ web address: www.kmuj.kmu.edu.pk

Email address: kmuj@kmu.edu.pk