

Importance of Serial C-Reactive Protein in Probable Neonatal Sepsis in RIMS

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Abstract: Sepsis is one of the commonest cause of increasing neonatal morbidity and mortality. It is responsible for about 30-50% of the total neonatal deaths in developing countries. Neonatal sepsis (NS) is a clinical syndrome of bacteremia characterized by systemic signs and symptoms of infections in the first month of life. The aim of this study is to determine the importance of serial measurement of C-Reactive Protein (CRP) in probable neonatal sepsis. It was a hospital based cross sectional study carried out in the department of paediatrics in Regional Institute of Medical Sciences (RIMS), Imphal, Manipur.

Keywords: C-Reactive Protein, Cross sectional study, Neonatal sepsis, serial measurement.

I. Introduction

Neonatal sepsis (NS) is a clinical syndrome of bacteremia characterized by systemic signs and symptoms of infections in the first month of life. The incidence varies from 1 to 4 per 1000 live births in Western countries. In India, neonatal septicaemia incidence varies from 11-24.5 per 1000 live births.¹

Globally of the 130 million babies born every year, about 4 millions die in the first 4 weeks of life, i.e. neonatal period. The main direct causes of neonatal deaths are estimated to be preterm birth (28%), severe infection (26%), and birth asphyxia (23%).² Probable sepsis in a neonate or infant having clinical picture and risk factors suggestive of sepsis and having a positive sepsis screen.³

Proven sepsis – in a neonate having clinical picture suggestive of sepsis along with either of the following (i) isolation of pathogens from blood or CSF or urine or abscess (ii) pathological evidence of sepsis on autopsy.³

NS can be classified into two major categories depending upon the onset of symptoms:

EOS: 0 – 72 hrs

LOS: > 72 hrs up-to 4 weeks

Risk factors for EOS:

Low birth weight or prematurity, Maternal fever within 2 weeks prior to delivery, Foul smelling and/or meconium stained liquor, Rupture of membranes > 24 hours, Single unclean or > 3 sterile vaginal examination(s) during labour, Prolonged labour (sum of 1st and 2nd stages of labour > 24 hours), Perinatal asphyxia (Apgar score < 4 at 1 minute).⁴

Risk factors for LOS:

- Low birth weight, Prematurity, Admission in intensive care unit, Mechanical ventilation, Invasive procedures. Causative organisms were found mainly from genital tract like E.coli, GBS, Klebsiella, etc.

Laboratory Diagnosis of neonatal sepsis

1. Haematological Parameter (Sepsis Screen)
 - a. White blood count < 5000/cu mm or > 18000/cu mm
 - b. Absolute neutrophil count – < 1800 cu mm
 - c. Band cell count and immature to total neutrophil ratio I/T > 0.2
 - d. Micro ESR > 15 mm in 1st hour
 - e. CRP > 10 mg/L
2. Blood, urine and CSF culture
3. Direct visualisation of bacteria by buffy coat smear
4. Chest X-ray
5. Lumbar puncture +/-

All neonates suspected to have sepsis should have a septic screen to corroborate the diagnosis. If two (or more) parameters are abnormal, it should be considered as a positive screen and the neonate should be started on antibiotics.⁵ If the screen is negative but clinical suspicion persists, it should be repeated within 12 hours. If the screen is still negative, sepsis can be excluded with reasonable certainty. For early onset of sepsis, documentation

of polymorphs in the neonatal gastric aspirates (> 5 per high power field) at birth could serve as a marker of chorio-amnionitis and it may be taken as one parameters of sepsis screen.⁵

Probable sepsis-in a neonate or infant having clinical picture suggestive of sepsis, the presence of any one of the following criteria is enough for assigning probable diagnosis of infection.(i) existence of predisposing factors –maternal fever or foul smelling liquor or prolonged rupture of membrane(>18 hours) or gastric polymorphs (>5 per high power field),(ii) positive septic screen (two of the four parameters namely, TLC(<5000 cu mm), band : total polymorphs ratio(>0.2), c-reactive protein (>10 mg/L) and micro ESR (> 15mm in 1st hours) (iii) radiological evidence of pneumonia.⁶

Proven sepsis – in a neonate having clinical picture suggestive of sepsis along with either of the following (i) isolation of pathogens from blood or CSF or urine or abscess (ii) pathological evidence of sepsis on autopsy.⁷ C-Reactive protein Phillipson in 1957 first described the presence of CRP in bacterial infection of neonates. Later on between 1962-1966 Fellix and Hanson in 1981 observed that CRP increased invariably in neonatal infection and more consistently with septicaemia and bacterial meningitis. The acute phase C-reactive protein (CRP) is synthesized in the liver in response to inflammatory cytokines and may increase 1000 folds during an acute phase response. Because of its short half life of 19 hours CRP levels can be expected to fall quickly after efficient elimination of the microbial stimulus. Thus CRP may sufficiently reflect the individual balance between the microbes and the immune system of the neonate for monitoring the effect of antibiotic treatment and for guiding the duration of antibiotic therapy.⁸

Serial determination of CRP is diagnostic and therapeutic tool. Any elevation of serum CRP in the neonate always represent endogenous synthesis, since it passes the placenta in exceedingly low quantities.⁸

CRP is composed by five identical subunits arranged in a cyclic pentamer shape. The whole protein has a diameter of 102 angstrom and molecular weight of 11800 Daltons. Ability to produce CRP does not appear to be affected by gestational age. Sensitivity is lower for gram positive than gram negative. Foetal distress, hyperbilirubinaemia, intraventricular haemorrhage can result in elevation of CRP.⁹

No single laboratory test has been found to have acceptably specific and sensitive for predicting infection. Therefore, the result of laboratory studies must be assessed in conjunction with the present of risk factors and clinical signs of sepsis. A label of more than 10 mg/L is consider as abnormal in the neonate. When CRP is negative at the onset of disease, it must be repeated after 12hrs. Accurate measurement of CRP can be made by laser nephelometry or single radio immune-diffusion assay.¹⁰ Blood culture – It is the gold standard for diagnosis of sepsis.¹⁰ Although a positive culture is obtained in 30-75% of the cases, it is the time consuming procedure and requires 48 – 72 hours should be performed in all cases of suspected sepsis prior to starting antibiotics. It is now possible to detect bacterial growth within 12 to 24 hours by using improved bacteriological techniques such as BACTEC and BACT/ALERT blood culture systems.⁹

Management:

Supportive: At the time of admission, prior to administration of antibiotics blood was collected and sent for sepsis screen and blood culture. He/she should be nursed in a thermo-neutral environment taking care to avoid hypo/hyperthermia. Oxygen saturation should be maintained in the normal range. If the infant is hemodynamically unstable, intravenous fluids should be administered and the infant is to be monitored for hypo/hyperglycaemia. Antimicrobial therapy- there cannot be a single recommendation for the antibiotic regimen of neonatal sepsis for all settings. The choice of antibiotics depends upon the prevailing flora in the given unit and their antimicrobial sensitivity. Decision to start antibiotic is based upon clinical features and /or a positive septic screen. However, duration of antibiotic therapy is dependent upon the presence of a positive blood culture and meningitis.

Adjunctive therapy-

Exchange transfusion, intravenous immunoglobulin, and granulocyte –macrophage colony stimulating factors may be considered.

II. Aims And Objects

To determine the importance of serial measurement of c reactive protein in probable neonatal sepsis.

III. Materials And Methods

3.1 Study design:cross sectional study

3.2 Study duration:October 2014 to September2016

3.3 Study setting:The study was carried out in the Dept. of Paediatrics in collaboration with the dept. of Microbiology, Regional Institute of Medical Sciences, RIMS, Imphal.

3.4 Sample size: A total of 100 cases were included in the study.

3.5 Study population: All live neonates from 1 to 28 days of life with clinically suspected sepsis presenting to the department of paediatrics, RIMS.

3.6 Inclusion criteria: All live new-borns up to 28 days of life presenting with following risk factors were included:

- Maternal fever, Foul smelling liquor, Prolonged labour, suspected neonates with signs and symptoms of sepsis (Temperature instability, feeding difficulties, respiratory distress, jaundice, convulsions, birth asphyxia).

3.7 Exclusion criteria:

- Parents/guardians denial for participation in study. Neonates who received antibiotics before admission. Neonates with major congenital malformation.

3.8 Study tools:

The study tools that were used in the study are as follows:

1. Infantometer
2. Plastic measuring tape (butterfly brand)
3. Calibrated meter ruler.

Statistical analysis: At the end of the study period, the observations were recorded in the suitable proforma. Data was analysed using SPSS version 21. Data collected was presented in percentages and for testing statistical significance, appropriate test like chi-square test was used.

5. Ethical issues: Ethical approval was obtained from the institutional ethics committee, RIMS, Imphal before beginning the study. Confidentiality was maintained.

IV. Results

Relation between CRP level measured baseline and after 24 hours among CRP positive and blood culture positive

CRP (mg/L) positive and blood culture positive	Mean ± SD	Paired t-test p-value
At admission	11.2 ± 2.3	t=-1.76
After 24 hours	12.3 ± 1.5	p-0.220

Among CRP positive and blood culture positive, at admission CRP level was 11.2 ± 2.3 mg/L but after 24 hours of treatment with antibiotics there was insignificant increase in CRP (p>0.05) which was 12.3 ± 1.5 mg/L.

Relation between CRP level measured baseline and after 24 hours among CRP negative and blood culture positive

CRP (mg/L) negative and blood culture positive	Mean ± SD	Paired t-test p-value
At admission	8.0 ± 2.5	t=-2.65
After 24 hours	9.5 ± 2.1	p-0.000

Among CRP negative and blood culture positive, at admission CRP level was 8.0 ± 2.5 mg/L but after 24 hours of treatment with antibiotics there was significant increase in CRP (p<0.05) which was 9.5 ± 2.1 mg/L.

V. Discussion

In this present study CRP was raised in 70% of cases. Mean CRP level was 11.6 mg/L with a standard deviation of 4.05 mg/L. Blood culture was positive in 55% of cases in this study. Accuracy of CRP in diagnosing neonatal sepsis was 57.8%. Among CRP positive and blood culture positive, at admission CRP level was 11.2 ± 2.3 mg/L but after 24 hours of treatment with antibiotics there was insignificant increase (p>0.05) in CRP which was 12.3 ± 1.5 mg/L. Almost similar finding was noted in the study by Setal SB et al.

VI. Conclusion

The results of this study shows that in patients with CRP positive at admission if the CRP is increased after 24 hours we can consider that the blood culture is most likely to be positive, so we should consider to continue antibiotics for full course. In those patients with CRP negative on 1st day, but blood culture positive their CRP was increased in due course, so we should consider to continue antibiotics for full course.

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