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VALUE OF C–REACTIVE PROTEIN IN NEONATAL SEPTICEMIA

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ABSTRACT

Objective — To assess the value of c-reactive protein as a diagnostic tool in neonatal septicemia, To find prognostic value of quantitative assay of serial CRP in neonatal septicemia and usefulness of serial CRP for guiding duration of antibiotic therapy in neonatal septicemia. **Research Design and Methods**— A total of 35 full-term neonates of birth weight >2.5 kg admitted in Nursery Balchikitsalaya RNT Medical College, Udaipur (Lodger and intramural) were included and undertook relevant routine investigation to assess the neonatal septicemia i.e. blood was taken for blood culture, blood cell count with differential and quantitative CRP and micro ESR. **Results**— C-reactive protein is having >90% sensitivity in diagnosis of neonatal septicemia as compared with other parameters of sepsis screening. A serial decline in CRP value has a strong positive correlation with duration of antibiotic therapy. ($P < 0.001$) **Conclusions**- C-reactive protein is highly sensitive test in diagnosis of neonatal septicemia.CRP estimation should also be done on day-4 i.e. after 72 hours of starting antibiotic therapy in a septic newborn. Persistently high values have prognostic implications and antibiotics should be changed if clinically justified. Serial CRP estimation have greater value as compared to single CRP estimation in judging the course and outcome of neonatal septicemia.

Keywords: C–Reactive Protein, Neonatal Septicemia, Blood culture, Blood cell count.

INTRODUCTION

Perinatal infection especially neonatal bacterial sepsis is the commonest cause of neonatal mortality and morbidity in India.Current neonatal mortality rate (NMR) of India is about 34/1000 live births.**(1)** Sepsis accounts for almost half of the deaths that occur during neonatal period. Globally WHO estimates 5 million neonatal deaths a year, infection contributes 30-40% of neonatal deaths globally.**(2)** Sepsis neonatrum is the completely curable life-threatening disease of the newborn. Prompt institution of specific anti-bacterial therapy can be life saving and can reduce neonatal morbidly and mortality up to a large extent.

Newborn is a relatively compromised host who is unable to localize the infection and bacterial sepsis can frequently involve vital organs including meninges. This results in non-specific subtle signs and symptoms, which intrigue even the most astute clinician, the two major problems which concern the neonatal physician are, Is it septicemia? And if confirmed as septicemia, whether the patient is improving? There is no rapid and reliable test for the confirmation of the etiologic diagnosis. The treatment is generally started when early

markers of neonatal infection (sepsis screen), support clinical picture.**(3)**

A number of acute-phase proteins serve as useful indicators of infection in the neonates viz. C-reactive protein, alpha-1 acid glycoprotein, heptoglobin, α-1 antitrypsin, fibrinogen, pre albumin, transferrin etc. These markers are still in a controversial status and none of them has until now established for clinical purpose.**(4,5)**

The best studied amongst them is C-reactive protein. C-reactive protein is synthesized in the liver in response to inflammatory cytokinines. Because of its shorter half-life of 19 hours, its level rises with inflammation and accurately parallel with the activity of the inflammation and quickly fall after efficient eliminations of the microbial stimulus. While a high CRP is of important role in diagnosis, treatment and monitoring of inflammatory disorders. Also serial decline in CRP with therapy is suggestion of adequate response to antibiotics and recovery.**(6)**

A level of >16 mg/L on day 1 and 2 of life and >10mg/L on subsequent day in the newborn period is considered as abnormal in neonates.**(7)**

A quantitative CRP by immune-turbidimetric test is most accurate, rapid and reliable method which will thus be directly indicating whether the neonate is having septicemia or not.**(8)**

Septicemia of newborn infants can be effectively treated by prompt intravenous antibiotic therapy. Once therapy has been initiated it is important to assess whether the chosen treatment is indeed effective. A successful treatment will be accompanied by a decline in CRP to normal (i.e. <10mg/L), while a rise in CRP beyond the third day of empirical treatment would give rise to a suspicion of ineffective antibacterial treatment or fungal infection. **(9)**

This study of exact quantitative CRP value is being planned to assess therapeutic response to antibiotics and to know the relation of prognosis to initial absolute levels.

MATERIALS AND METHODS

A total of 35 full-term neonates of birth weight >2.5 kg admitted in Nursery Balchikitsalaya RNT Medical College, Udaipur (Lodger and intramural) were included. The study was carried out during the month of March to May of year 2006. Permission was taken from the Institutional Ethics Committee. Inform consent was taken from parents of neonates.

Inclusion criteria were:

- Symptoms and signs suggestive of septicemia with positive sepsis screen.**(10)**

Exclusion Criteria

- Neonates with birth asphyxia (APGAR score <5 at 5 minutes).
- Neonates with Meconium aspiration syndrome.
- Neonates who had previously received antibiotics in any form.
- Patient undergoing surgery or major chromosomal / congenital malformation.
- Neonates <1.5 kg and gestational age <28 weeks.

Procedure

After the first clinical suspicion of infection, blood was taken for blood culture, blood cell count with differential and quantitative CRP and micro ESR. Antibiotic therapy with a standard regimen of Ampicillin/Cefotaxim and Gentamycin/Amikacin was started in all neonates with suspension of septicemia. Sepsis screen was done on the time of admission i.e. 0 hours and then again at 4^{th} day i.e. after 72 hours and again on 8^{th} day i.e. 168 hours and if sepsis screen is not negative on 8^{th} day then again on 14^{th} day. Hence a total of three or four value of CRP in all selected neonates were known by quantitative assay (immunoturbidimetric method). **(8)**The initial CRP level and their rate of fall studied and correlated with outcome of neonates. Antibiotics were stopped whenever CRP levels are <10mg/L. If CRP value on day

4th was not less than initial value or have increased than the previous value, antibiotics were changed. The response to changed therapy further reassessed on day 8th similarly. The neonates were also evaluated clinically daily and CRP levels correlated with clinical response. CRP is an immune-turbidimetric test for quantitative determination, based on micro particles coated with anti-human CRP. CRP present in the sample reacts with the micro particles and the resultant change in the turbidity of the solution is measured by the photometric method in term of optical density. The reagents are pre calibrated and calibration provided with each kit.

RESULTS

A total of 35 term neonates (wt >2-5kg) lodger and intramural were included in the study, out of which 25 (71.4%) were male and 10 (28.6%) were female neonates (Table No. 1). The mortality was highest 5 (20%) in male group and 1 (12.5%) was in female group. 18 cases (51.43%) were of early onset type (<72 hrs) and 17 cases (48.57%) were late onset type (>72 hrs). Further, 5 cases (27.78%) expired in early onset group and one case (5.26%) expired in late onset group. This is statistically significant ($p<0.05$). 91.4 % of cases were in between 2.56-3.8 kg and 8.6% of cases were >3.8 kg the mortality according to weight had no significant correlation (P value > 0.05).

More than three forth (77%) were delivered outside the hospital i.e. lodger and 23% were intramural. Mortality statistics showed that death was also more in lodger group i.e. 5 cases (18.57%) as compared to intramural 1 (12.5%).

Considering the presence of maternal risk factors and occurrence of neonatal septicemia showing that history of >3 per vaginal examination was the most important risk factor for developing neonatal septicemia. It was present in 42.85% of cases followed by PROM >12 hrs in 12 cases (34.28%). This revealed the fact that frequent per vaginal examination is associated with more chance of neonatal septicemia. Refusal to feed was commonest presenting symptoms (100%) and poor sucking /swallowing was commonest sign (85.7%).

Table no 1 showing Blood cultures were positive in 14 cases (40%) and were negative in 21 (60%) cases. 21.4% deaths were in culture positive and 14.35% in culture negative group respectively. The regression analysis revealed statistically significant correlation between mortality and culture positivity. The CRP value on Day-0 also well correlated with culture positivity. In 14 cultures positive cases CRP on Day 0 were also positive in 13 out of 14. This indicates a strong correlation between CRP positivity and blood culture positivity.

The detailed CRP quantitative analysis on Day-0, Day-4, Day-8 and Day-14 revealed many unexpected results and at the same time many superficially coherent result were found to be statistically insignificant.

Table-2 also showing sepsis screening done on admission including all eight parameters (micro ESR, TLC, ANC, I/T Ratio; platelet count, PBF, CRP and Blood culture). This table revealed the sensitivity in diagnosis of neonatal septicemia of different parameters. Out of them alone CRP on Day-0 had the sensitivity of 91.42% which was maximum as compared with the other parameters individually. This fact is statistically highly significant ($p<0.05$).

Next to CRP the highest sensitivity was of PBF (Toxic granules present/absent) (68.57%) and micro ESR (65.7%). This shows the diagnostic value of C-reactive protein (sensitivity >90%) in neonatal septicemia.

Table 2 showing the correlation between Day 0 CRP value and TLC, ANC, I/T ratio, platelet count, PBF and micro ESR. Day 0 CRP value was negatively correlated with TLC (r value = -0.02), ANC (r value = -0.02) and platelet count (r value = -0.03). This indicates that in neonatal septicemia as CRP value increase TLC, ANC, a

platelet value decrease which usually occurs in neonatal septicemia.

Day 0 CRP and value BCC, I/T Ratio micro ESR were positivity correlated (r value = 0.04, 0.01, 0.14 respectively). This indicates that along with C - reactive protein BCC, I/T ratio, micro ESR also increases. The CRP values were recorded from a minimum of 10mg/L to a maximum of 50 mg/L on day of admission (Day-0).

The Day 0 CRP value did not correlate well with the overall mortality of the patient. Though the Day 0 CRP value not help in prognosticating survival of a septic newborn, the Day 4 CRP (i.e. after 72 hrs. of therapy) correlated well with mortality statistics. The raised CRP and Day 4 after starting therapy were strongly related to chances of mortality. Hence after starting antibiotic therapy in a septic newborn, he was assessed daily and biochemically on Day 0, Day 4, Day 8 and Day 14 and raised CRP values on Day-4 signified high chances of mortality.(Table no 3)

We also observed that there is a significant fall in CRP value from Day 0 to Day 4 Day 8 and Day 14 Figure 1 shows that the average CRP value of Day 0 in all the patients was 22.83 mg/l. while the Day 0 CRP value in patients which died was 23.0 mg/l. The average was not related in any significant manner.

The rate of all from Day-0 to Day-4 was 0.10 mg/L/hr and from Day 4 to Day 8 was 0.06mg/L/hr and from Day 8 to Day 14 were 0.02 mg/L/hr.The average CRP value on Day 4 Day 8 and Day 14 were 17.05 mg/l, 9.58 mg/l and 6.52 mg/l respectively. (graph).

DISCUSSION

Bacterial infection of newborn infants can be effectively treated by prompt IV application of antibiotic drugs. Once therapy has been initiated, it is important to assess whether chosen treatment regimen is indeed effective. Ideally, the parameters used to monitor the treatment response should be specific for bacterial infection. It has been shown in previous studies that the acute phase protein i.e. C-reactive protein (CRP) fulfills these criteria to a large extent. **(11)** Serum CRP levels can rise more than 1000 fold in response to bacterial infection and decrease after antibiotic treatment has been initiated. **(12)** CRP is therefore frequently used in combination with other clinical and laboratory parameters to monitor the individual response to antibiotic treatment. Normal CRP level in neonates as per National Neonatal Perinatal Database (NNDP) are 16 mg/L on day 1st and 2nd of life and 10 mg/L as subsequent days of life.**(13)**

This study intended to correlate the CRP value at the time of admission to the final outcome of the particular newborn, to study the serial decline of CRP to assess the prognostic value of CRP in neonatal septicemia. The study was also designed to assess the usefulness of serial CRP for guiding duration of antibiotic therapy in neonatal septicemia.

Comparing the present study by the study of 1982 (Yentis et al) which concluded that a decreased CRP by 25% or more from previous level is a good indicator of resolution of sepsis,**(9)** we also observed that there is a significant fall in CRP value from Day 0 to Day 4 Day 8 and Day 14 (Figure no 1.graph).

The strongest support to present study is found in comparison to Rønnestad and Abrahamsen et al (1999) who proved that microbial treatment failure presented by , a moderate high level of CRP before starting the treatment and increased continuously thereafter whereas a successful treatment was usually noted by a serial decline in CRP value in within 4 days.**(14)**

CRP is a very helpful marker for showing duration of antibiotic therapy in suspected neonatal septicemia. In this study we did sepsis screening of a case of suspected neonatal septicemia on day 0. When more than two parameters were positive we considered it a case

of neonatal septicemia. We follow this care for 14 days clinically as well as by laboratory by doing sepsis screen after 4 day, after 7 days and after 14 days. Antibiotic therapy was stopped as soon as CRP returned to within normal range (< 10mg/l). The mean treatment duration was 11.30 days median was 14 days and range was 4-21 days.

Figure No.1 shows that CRP declined rapidly after initiation of antibiotic therapy. This allowed discontinuation of antibiotic treatment after mean of 11.3 days (median 14 days, range 4-21 days). One patient was treated for 21 days because of persistence of elevated CRP beyond 14 days.

In bacterial infection of the newborn, the interaction between a bacterial pathogens and the immune system of the neonates is likely to be individually variable. Some infects confronted with a low bacterial burden will eliminate the pathogen earlier and require less antibiotic support than others, who are infected with a more virulent strain or are in some way immuno compromised, require long antibiotic support. This individualized are guided approach may be more appropriates, than treating infected infants for a fixed time interval.

At the same time, comparing present study to a study of Ulm, Germany (Stephan Ehl et al, 1997) are concluded the same results i.e. CRP is a first-class and independent indicator for deciding the duration of antibiotic treatment in a major subgroup of newborns with suspected bacterial infection. This approach would allow considerably shorter course of antibiotic therapy.**(15)**

Inspite of all these results present study has some limitation that need careful consideration .First the results are only valid for specified subgroup of term neonates of greater than 2.5 Kg birth weight without central catheter. However this subgroup presents the majority of neonates receiving antibiotic treatment. Our results are based on the specific pathogens prevalent at our institution. Therefore extrapolation of these data to other institutions should be done with great care. The incidences of positive blood culture in this study were relatively low. The sample size of the study was small.

CONCLUSION

C-reactive protein is highly sensitive test having >90% sensitivity in diagnosis of neonatal septicemia as compared with other parameters of sepsis screening.CRP estimation should also be done on day-4 i.e. after 72 hours of starting antibiotic therapy in a septic newborn. Persistently high values have prognostic implications and antibiotics should be changed if clinically justified. Serial CRP estimation have greater value as compared to single CRP estimation in judging the course and outcome of neonatal septicemia.CRP guided approach should be used regarding duration of antibiotic therapy than treating neonatal septicemia for a fixed time interval.

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Table No. 1 Sepsis Screening Parameter Positivity on D_0, D_4, D_8 and D_{14}

Parameter	No. of cases positive			
	D_0	D_4	D_8	D_{14}
Raised Micro ESR (>15mm in 1st hr.) or >(age +3) in 1st hr in < 3 days old	23 (65.7%)	16	6	1
TLC (<5000 or >20,000 cumm)	5 (14.3%)	2	0	0
ANC (<1,500 cumm)	0	0	0	0
I /T Ratio (> 0.2)	22 (62.6%)	23	18	4
Platelet count (< 1.5 /cumm)	14 (40%)	14	4	0
PBF (Toxic granules Present / Absent)	24 (68.57%)	26	5	0
*CRP >16 mg/dl m 1st & 2nd day > 10mg/l on subsequent days	32 (91.42%)	26	12	1
Blood culture	14 (40%)	-	-	-

*CRP alone had highest sensitivity in diagnosis of neonatal septicemia.

Table No. 2 Table showing Correlation between Day 0 CRP value and TLC, ANC, I/T Ratio, Platelet count, PBF and Micro ESR

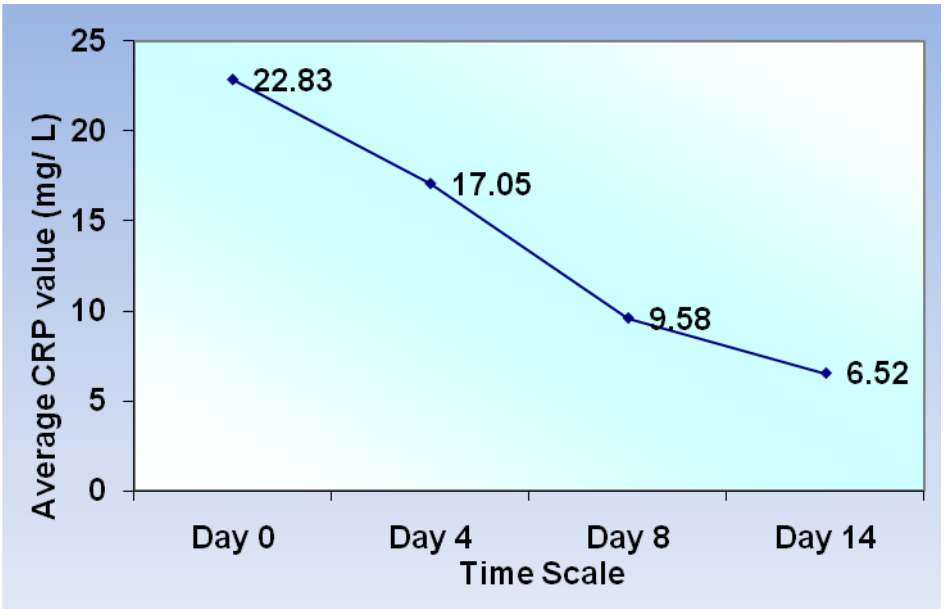
	Correlation Coefficient (r)	P value
TLC	-0.02	NS
Band cell count	0.04	NS
ANC	-0.02	NS
I /T Ratio	0.01	NS
Platelet count	-0.03	NS
Micro ESR	0.14	NS

Table No. 3 Table showing Correlation between Day 0, Day 4, Day 8, Day 14 of CRP values with Duration of Antibiotic Therapy

	Correlation Coefficient (r)	P value
D0	0.07	NS
D4	0.27	<0.05
D8	0.37	<0.01
D14	0.67	<0.001

*A serial decline in CRP value has a strong positive correlation with duration of antibiotic therapy

Figure No. 1 Average Rate of fall of CRP



*Average CRP on Day 0 – 22.83 mg/L (rate of fall was 0.10 mg/L/hr from Day 0 to Day 4)
*Average CRP on Day 4 – 17.05 mg/L (rate of fall was 0.08 mg/L/hr from Day 4 to Day 8)
*Average CRP on Day 8 – 9.58 mg/L (rate of fall was 0.06 mg/L/hr from Day 8 to Day 14)
*Average CRP on Day 14 – 6.52 mg/L