

Study of C-reactive protein in healthy neonates

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Abstract

Introduction: C-reactive protein is widely used marker for early detection of neonatal sepsis. There is reported wide variation in normal CRP level of new born as well as its sensitivity and specificity regarding its use as an indicator for sepsis. It is known that cascade of events in sepsis leading to rise of CRP may take few hours to days to increase; therefore predictive value is higher after 24 to 48 hours of infection. Considering the above factors this work was taken to know the normal pattern of CRP during initial days of birth in healthy neonates & to have a cut off value. **Materials and Methods:** The present study was conducted in association with pediatric & biochemistry department in IMS & SUM Hospital, Bhubaneswar to observe normal CRP level during zero hour (cord blood) and 48 hours in apparently healthy new born babies. Babies having perinatal asphyxia and other severe complications and babies of mother with preexisting chronic diseases were excluded from the study. CRP was estimated by turbidometry method. Data were collected and analyzed with appropriate statistical application. **Results:** After excluding babies as per exclusion criteria, finally 48 new born data were included for study and analysis. Upper reference value for CRP at birth & at 48hrs was established. CRP value was small in cord blood healthy newborn babies. There is significant rise in CRP by 48hrs compared to that at birth. Maternal problems like PROM, perinatal fetal distress and gestational hypertension affected CRP positively. **Conclusion:** Maternal and fetal factors can affect the neonatal CRP value and should be kept in mind while considering CRP as an indicator of sepsis.

Key words: CRP- C-reactive protein, PROM- premature ruptures of membranes, healthy neonates

Introduction

As we all know that early neonatal sepsis is a known difficult problem for diagnosis. CRP is a known marker commonly used for early detection of neonatal sepsis in nursery. There is reported wide variation in normal CRP level of newborns as well as its sensitivity & specificity regarding its use as indicator of sepsis. The fear of missing a case of neonatal septicemia leads to overuse of antibiotics. In addition to infections, CRP has been shown to be elevated in non-infectious conditions in neonates including meconium aspiration, respiratory distress syndrome, fetal hypoxia and intraventricular hemorrhage [1].

Different cut-off values for raised CRP have been suggested by various studies using varying protocols [2]. Although several studies confirm that CRP levels are useful in the early diagnosis of sepsis, there are reports

to the contrary [3-6]. It is known that cascade of events in sepsis leading to rise of CRP may take few hours to days to increase; therefore predictive value is higher after 24 to 48 hours of infection. Considering the above factors this work was taken to know the normal pattern of CRP during initial days of birth in healthy neonates & to have a cut off value.

Materials & Methods

The present study was conducted in association with pediatric department & biochemistry department in IMS & SUM Hospital, Bhubaneswar during January to May 2016.

Inclusion Criteria

Healthy term (>37 weeks) & near term babies (34-37 weeks) born in hospital without significant risk factors for sepsis or severe asphyxia.

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Exclusion Criteria

Mothers having

- Chronic diseases like Diabetes mellitus, Tuberculosis, Syphilis.
- Overt infection (fever >101.6 °F for 2 days, foul smelling liquor or any other infection).
- Prelabour rupture of membrane.
- Untreated/partially treated urinary tract infection in the antenatal period .

Babies

- Born <35 weeks of gestational age
- 5 min APGAR score <3/10
- Babies who became sepsis screen positive (at least two criteria of sepsis)
- Babies who developed clinical features of sepsis needing antibiotic therapy during hospital stay
- Babies who had an early discharge without screen

Sample size estimation:Cord blood samples were collected from 64 babies. After excluding babies as per exclusion criteria 48 valid cases were included for study & analysis.

Laboratory method:Approximately 5ml of blood was collected from the umbilical cord after clamping & cutting of the cord. About 48hrs after birth, approximately 2ml of blood was collected by venipuncture from the newborn. Samples were transported without any delay to the laboratory for CRP estimation. CRP was estimated by turbidometry method.

Data collection and analyses:CRP value was calculated at birth & 48hrs after birth. Newborn babies were observed for signs of sepsis for at least 48h. Clinical data were collected using a questionnaire. Data were analyzed using SPSS software. For all statistical analyses the p value was considered to be significant at $p < 0.05$

Results

Table 1: Distribution of mothers according to age, parity and mode of delivery.

	Age				Parity			Mode of delivery				
	<25 yrs	25-35 yrs	>35 yrs	Total	Primi	Multi	Total	NVD	ANVD	Em LSCS	EI LSCS	Total
No.	18	27	3	48	18	30	48	20	15	5	8	48
%	37.5	56.2	6.2	100	37.5	62.5	100	41.6	31.2	10.4	16.6	100

This table shows distributions of mothers whose babies blood CRP were studied according to age, parity and mode of delivery. The samples were collected from babies of all age groups of mothers and there is normal distribution of samples and maximum mothers were in the age group of 25-35 years. The parity wise distribution of mothers show normal distribution and most of the mothers were multiparous. This table also signifies babies were distributed normally in all categories of delivery.

Table 2: Analysis of CRP in cord blood & at 48 hrs.

	Cord blood (0hr) n = 48	CRP (48hrs) n = 48
MEAN (mg/L)	3.362	7.400
SE (MEAN)	0.065	0.400
MEDIAN (mg/L)	3.320	6.050
MODE (mg/L)	3.000	6.000
SD	0.455	2.770
Skewness	1.580	1.320
SE/Skewness	0.340	0.343
Kurtosis	2.659	1.510
SE Kurtosis	0.674	0.670
Range	2.000	13.000
Minimum (mg/L)	3.000	3.000
Maximum	5.000	16.000

In our study the mean value of CRP at 0hr was 3.362 mg/L with a SD of 0.455 & median value that is 50th percentile was 3.2 mg/L. Similarly at 48hrs mean CRP value was 7.400 mg/l with SD of 2.77 & median 50th percentile value was 6.050 mg/L. This shows a wider variation due to wider difference between maximum & minimum value at 48 hrs which is between 3 & 16. Since the median value is 6.050. This is the most probable correct value. All values hovers round this.

Table 3: Analysis of CRP in cord blood & at 48 hrs.

Percentile	mg/L Cord blood (0 hr) n=48	mg/L 48 hr n=48
25 th	3.00	5.40
50 th	3.20	6.05
75 th	3.60	8.15
95 th	4.36	13.10

This slide shows percentile distribution of CRP values at 0hr & 48 hrs. The 50th percentile or median value at 0hr 3.20mg/L & at 48hrs was 6.05mg/L. The maximum value that is 95th percentile obtained at 0hr 4.36mg/L & at 48 hrs 13.10mg/L. As the maximum value 95th percentile at 48hrs was 13.10mg/L. This shows wide variation of CRP value in some cases. That means value can rise up to 13mg/L even if sepsis is not there. But median value was 6.05mg/L around which most of the values were found. This is the most probable correct value at 48 hrs.

Table 4: Comparison of mean CRP at birth& 48 hrs.

MeanDifference	3.78
SD	2.72
SE	0.393

This is comparison of mean value between 0hr & 48hrs with a mean value difference 3.78, SD 2.72 & 95% confidence interval between two mean values 2.99-4.57. Paired t-test when applied to these two sets of values at 0hr & 48hrs showed t value 9.6 with a 2 tailed significance < 0.01. This shows significant difference between CRP values at 0hr & 48hrs in healthy neonates.

Table 5: Sex wise distribution of CRP values.

Sex	N (%)	0 ^{hr} Mean±SD	48hr Mean±SD
Male	20 (41.6)	3.57±0.81	6.36±1.34
Female	28 (58.3)	3.88±0.67	7.33±2.39
Paired t-test		P=0.19 (insignificant)	P=0.25 (insignificant)

This shows distribution of CRP value in accordance with the sex of the baby. Sex has no effect on CRP value as P value is insignificant.

Table 6: CRP values in different gestational age.

Gestational age	N	Cordblood		48 hrs	
		Mean	SD	Mean	SD
Near term (35-37 wks)	15	3.28	0.51	7.18	1.11
Term (37 wks)	33	3.4	0.84	7.09	1.8
Paired t test		P=0.42		P=0.24	

This table shows analysis of CRP values between near term & term babies. This signifies gestational age doesn't affect CRP value.

Table 7: Linear regression analysis for confounding factors in CRP.

	N	Cord blood Mean±SD	48hrs Mean±SD	Regression Coefficient
5 min. APGAR<5	6	3.6	7.3	1.52 (P<0.01)
PROM (>48hrs) with sepsis screen negative	7	3.43	7	1.32 (P<0.05)

This table shows linear regression analysis to see the influence of factors to see the influence of factors like low APGAR & PROM over CRP value at 48 hrs. In our study there was positive correlation of factors like 5 min APGAR<8 and PROM (>18hrs) with the neonatal CRP at 48hrs. CRP value could be up to 1.52 times when APGAR<8 and in PROM (>18hrs) up to 1.3 times. This can be shown in the linear regression analysis for confounding factors. That may not be suggestive of sepsis when considered as single criteria.

Discussion

It is generally acknowledged that neonatal sepsis remains an important diagnostic consideration in many infants [7]. CRP rises in response to inflammation or tissue necrosis [8]. Although it is a nonspecific marker, it has repeatedly shown to increase with bacterial sepsis & meningitis [8, 9,10-12]. So it is difficult to ignore use of antibiotic during early neonatal period. The present study was designed to evaluate the normal pattern of CRP during initial days of birth in healthy neonates & to have a cut off value.

In our study CRP value is small in healthy babies at birth with a median value of 3.2mg/L & 95th percentile of 4.36mg/L. CRP value significantly increases in first 48hrs of life in healthy babies with a median value of 6.05mg/L & 95th percentile of 13.10mg/L. This shows wide variation of CRP value. CRP value can rise up to 13.10mg/L even if sepsis is not there. Wasunna et al found no evidence that intraventricular haemorrhage was associated with elevation of CRP in neonates with no evidence of infection [13]. Schouten- Van Meeteren et al demonstrated no significant difference between the CRP levels of neonates with perinatal asphyxia, prolonged rupture of membranes, hyperbilirubinemia or respiratory distress syndrome, and those of a control group [14]. Xanthou et al also found no difference between the CRP levels in neonates with asphyxia compared to controls [15]. Gestational maturity & sex of baby did not influence the cord blood CRP or CRP at 48hrs. Chiesa et al showed that mean CRP concentration at birth was increased by a factor of 1.50 (95% CI, 1.32 to 2.03) if the 5-min Apgar score was <8 and by a factor of 1.32 (95% CI, 1.07 to 1.61) if the time from rupture of membranes was >18 hours [16]. This effect on CRP was no longer present by 48 hours of life. In our study CRP concentration at 48hrs was increased by 1.52 times if the 5 min APGAR score was <8 & by a factor of 1.3

times if the time from rupture of membrane was >18hrs. But this may not be suggestive of sepsis when considered as single criteria. CRP value can rise by 48 hrs compared to that birth even if sepsis not there. So CRP taken alone has a negative predictive value rather than positive predictive value.

Conclusion

CRP is most widely & extensively used marker of neonatal sepsis. Intrapartum risk factors for early onset sepsis can cause elevation of cord & neonatal CRP levels in the absence of infection. Maternal & fetal factors should be kept in mind while considering CRP as an indicator of sepsis.

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