Academic Journal of Medical Sciences
ISSN: 2708-2725
ORIGINAL ARTICLE

C-Reactive Protein as an Indicator in Early Neonatal Sepsis in Preterm

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Funding information
Self-funded

Conflict of interest
None declared by author

ABSTRACT

Background: *Despite increasing knowledge of pathophysiology and modern therapeutic approaches, the morbidity and mortality associated with early neonatal sepsis remains alarmingly high.*

Objective: *To evaluate the effectiveness of serial C-Reactive Protein and its rising titer in comparison with complete blood count and blood culture as screening tool for diagnosing early neonatal sepsis in preterm.*

Methods: *This study included fifty preterm neonates with clinical suspicion of early onset sepsis who admitted to the NCU of Al-Yarmouk Teaching Hospital in Baghdad. All were investigated at birth for CRP with titer and at 72 hours of life for second CRP. Complete blood count and blood culture also sent at 72 hours of life after notification to the changes in CRP titer and comparsion done between the results.*

Results: *Early onset sepsis was found to be more common in males, very low birth weight and in very preterm infants. Confirmed sepsis with positive blood culture were 30% of studied preterm neonate .C-reactive protein sensitivity was 73%, specificity was 40% while accuracy showed 50% with no significant association between rising CRP, blood culture and CBC abnormalities in the current study.*

Conclusion: *Rising CRP titer does have a role in the diagnosis of early neonatal sepsis in preterm but it is not specific enough to be the only indicator.*

Received *: August, 2023*

Published*: September, 2023*

DOI: 10.5281/zenodo.8352392

Keywords: *C-Reactive Protein, complete blood count, blood culture and sensitivity.*

1. INTRODUCTION

Globally, although the progressing development in the maternal and neonatal healthcare, infections continue to be a prevalent and significant contributor to morbidity and mortality among neonates and infants. According to available data, a notable proportion of fetuses, estimated to be as high as 2%, have in utero infection. Additionally, the prevalence of infections among neonates during the first month of life can reach up to 10%. According to the World Health Organization (WHO), four million newborn children die each year during the first four weeks of their lives. Of these, 75% die prematurely during the first week of life. The major causes of neonatal deaths globally were estimated to be infections (35%), preterm births (28%), intrapartum related complications (24%), and asphyxia (23%). Sepsis is the commonest cause of neonatal mortality and is probably responsible for (30-50%) of the total neonatal deaths each year in developing countries (1–3).

Neonatal period: is defined as the 1st 28 days after birth and may be further subdivided into the very early (birth to <24 hours) early (birth to <7 days) and late neonatal periods (7 days to <28 days) (1,4).

Preterm neonate : Live born infants delivered before 37 weeks from the 1st day of the last menstrual period, very preterm (28-33+6 weeks) and late preterm (34-36+6 weeks). (1,5)

Sepsis:

Neonatal sepsis is a clinical syndrome of systemic illness with or without accompanying bacteremia occurring in the first month of life, can be classified into two major categories depending on the onset of symptoms (5,6):

1.*Early onset neonatal sepsis* (EOS) : Which occurs mainly in less than 72 hours of neonatal life and up to 7 days (7,8).

2. *Late-onset sepsis (LOS)* : which occurs from 8 to 28 days of neonatal life, usually occurring in a health (4,9). Sepsis can also defined as the Systemic Inflammatory Response Syndrome (SIRS) to an infectious process which is manifested by 2 or more of the following conditions:

1. Temperature instability <35°C or >38.5°C

2. Respiratory dysfunction: Tachypnea >2 SD above the mean for age , Hypoxemia (PaO2 <70 mm Hg on room air)
3. Cardiac dysfunction: Tachycardia >2 standard deviation (SD) above the mean for age, Delayed capillary refill >3 sec and Hypotension >2 SD below the mean for age
4. Perfusion abnormalities: Oliguria (urine output <0.5 ml/kg/hr), Lactic acidosis (elevated plasma lactate and/or arterial pH <7.25) and altered mental status
5. Abnormal White Blood Cells count (WBC): Leukocytosis (WBC >19,000 /mm3) or Leukopenia (WBC < 6000 /mm3) with (ANC < 1800/ mm^3) and Immature to total neutrophil ratio of > 20%)
6. CRP (more than 1 mg/dl)
7. ESR (15 mm or more in the first hour of life) (1,10,11).

The susceptibility of the neonatal infant to infection is associated with the underdevelopment of the immune system upon birth. In the context of neonatal health, it is noteworthy that the transfer of IgG antibodies across the placenta, which primarily occurs during the third trimester of pregnancy, offers passive protection against some pathogens. This phenomenon is particularly relevant for preterm neonates. Preterm newborns, particularly those delivered prior to 30 weeks of gestation, exhibit a deficiency in the quantity of passively acquired antibodies (4,12).

The susceptibility of preterm newborns to invasive infection is inversely associated with the function of neutrophil; it increases by a decrease in neutrophil function and low amounts of immunoglobulins. Group B streptococci (GBS), Escherichia coli (E. coli), herpes simplex virus (HSV), Cytomegalovirus (CMV), varicella-zoster virus (VZV), respiratory syncytial virus (RSV), entero-viruses, and Candida species are recognized as significant pathogens during the early neonatal life . The estimated incidence of early-onset sepsis (EOS) is roughly 1 to 2 cases per 1,000 live birth. Higher incidence rates reported among premature neonates , and the incidence might be twice that in mature infants , with the highest rates observed in very low birth weight (VLBW) infants weighing less than 1,500 grams. Recent studies have reported a range of 15 to 23 cases per 1,000 VLBW births (1,12–14).

2. METHODOLOGY

The current prospective, single center study was carried out over a period of 5 months from the 1st of June 2018 to 31st of October 2018 in the neonatal care unit of Al-Yarmouk Teaching Hospital In Baghdad ,Iraq.

Inclusion criteria:

All patients admitted to the NCU of Al-Yarmouk Teaching Hospital during the period of our study, who were in the first day of life and less than 37 weeks, with any of the following signs of sepsis :

1. Temperature instability hypothermia (temp <35°C).
2. Respiratory symptoms: tachypnea (RR > 60 cycles/ min), dyspnea, grunting.
3. Cardiac symptoms: dyspnea, cyanotic attacks.
4. Gastrointestinal symptoms: abdominal distention, vomiting (bile stain).
5. Neurological symptoms: fit, lethargy, poor feeding, irritability.
6. Hematological symptoms: coffee ground vomiting.
7. Skin: sclerema.
8. Prolong rupture of membrane

Exclusion criteria:

1. Multiple congenital anomalies.
2. Underlying surgical conditions.

Initially eighty-four preterm infants met these criteria, but only fifty of them finish the study The thirty-four preterm infants excluded early from the study, twenty-two of them not fulfilled the criteria, while the remaining eleven were dead before the third day of their lives. The procedure that we followed was to take peripheral blood sample at birth (within the first 24 hr of life) for the first CRP with titer and at 72 hr of life for the second CRP with titer, CBC and Blood C&S.

Blood samples collected for CRP by draw two ml of blood into EDTA tubes and spun at 600 rpm for 20-40 min in a refrigerated tabletop centrifuge to separate serum, then kept one ml of serum at deep freezing at -20C with weekly collection of samples and were taken to a laboratory, the procedure was (Nephelometry) by using the instrument (Genrui).

Each neonate was examined by pediatrician and followed with in the first 72hr for EOS.

Patients were divided into 3 main groups:

1. Confirmed sepsis (patients with clinical signs and symptoms with positive blood cultures).
2. Suspected sepsis (patient with clinical signs and symptoms and / or positive sepsis screen).
3. No sepsis (patients with negative septic screen). CRP levels > 10 mg/dl considered positive according to the normal range of the kit that was used in the study.

Statistical analysis:

Statistical package for social sciences version 24 (SPSS v24) used to analyze data. Continuous variables presented as means with standard deviation and discrete variables presented as numbers and percentages.

Test performance was tested using indicators of screening test performance, namely; sensitivity, specificity, accuracy predictive value for positive test and predictive value for negative test with their confidence intervals.

3. RESULTS

Out of the fifty preterm neonates included in our study, males were twenty-eight cases (52.0%) and females were twenty –two cases (48.0%), gestational age very preterm from 28-33+6 wk were thirty cases (60.0%), late preterm from 34-36+6 wk were twenty cases (40.0%), birth weight VLBW < 1500g were twenty-seven cases (54.0%), LBW 1500- 2500g were twenty-three cases (46.0%), and history of maternal PROM were eleven cases (22.0%) as in (**Table 1**). According to the clinical features of our patients, dyspnea and grunting were observed in forty-six cases (92.0%), tachypnea in forty-one cases (82.0%), skin sclerema were five cases (10.0%), cyanosis were three cases (6.0%), poor feeding and lethargy were three cases (6.0%), Coffee ground vomiting were three cases (6.0%), Hypothermia were two cases (4.0%), fit was one case (2.0%), irritability was one case (2.0%), bilious vomiting after exclusion of surgical cause was one case (2.0%) as in (**Table 2**). According to markers of sepsis that included in our study fifteen preterm neonates were with positive blood culture and sensitivity (30%), S. epidermides was four cases (8.0%), S. aureus was three cases (6.0%), Acinetobacter spp was three cases (6.0%), Staphylococcus Saprophyticus (S. Saprophyticus) was two cases (4.0%), Gram neg. bacteria was two cases (4.0%),

Pseudomonas Spp was one case (2.0%). Out of fifty patients four of them had positive CRP at birth (8.0%), twelve of them had a positive CRP at 72h of their life (24.0%), while rising titer of CRP between the two reading were thirty-two (64.0%). According to CBC result WBC was normal in forty cases (80.0%), leukopenia was seven cases (14.0%), leukocytosis was three cases (6.0%), neutrophils were normal in forty cases (80.0%), neutropenia was nine cases (18.0%), neutrophilia was one case (2.0%), lymphocytes were normal in eighteen cases (36.0%), lymphcytopenia was twelve cases (24.0%), lymphocytosis was twenty cases (40.0%), platelets were normal in thirty-nine cases (78.0%), thrompocytopenia was eleven cases (22.0%), while no lymphocytosis was detected in our data as in (**Table 3**). Infants included were classified according to the results in to 3 major groups confirmed sepsis, suspected sepsis and no sepsis, and their association with the results of CRP at birth, at 72 h and its increasing titer which show no significant associations between them as demonstrated in (**Table 4**). The association between the blood culture results and the presence of rising CRP titer in studied premature neonates and we found also no significant association between rising CRP titer and results of blood culture, so rising CRP titer with positive blood culture were eleven cases (73.3%) and with negative blood culture were twenty-one cases (60%), while no rising in CRP with positive blood culture were four cases (26.7%) and with negative blood culture were fourteen cases (40%). Confirmed EOS more in male ten cases (66.7%), while female five cases (33.3%), and more common in VLBW eight cases (53.3%), while in LBW seven cases (46.7%), and also more common in very preterm nine cases (60%), while in late preterm six cases (40%), the percentage of each organism in blood C&S show s. epidermides (26.7%), staph aureus and acinetobacter spp., each of them (20%), s. saprophyticus and gram neg. bacteria each of them (13.3%) and pseudomonas spp.(6.7%), the clinical features of patients of confirmed sepsis calculated which show respiratory difficulties (dyspnea, grunting with or without tachypnea) the most common presented features which represent eleven cases (73.3%),lethargy and poor feeding three cases (20%), while hypothermia the least common one case (6.7%), also the outcome of our patients with confirmed EOS was seven cases on head box or mask (46.7%), on CPAP six cases (40%), while on ventilator only two cases (13.3%) as demonstrated in (**Table 5**).

Table 1. Characteristics of studied premature neonates

Variable		No.	%
Gestational Age (weeks)	$28 - 33^{+6}$	30	60.0
	$34 - 36^{+6}$	20	40.0
Birth weight (gram)	< 1500 (VLBW)	27	54.0
	1500-2500 (LBW)	23	46.0
Child Sex	Male	28	56.0
	Female	22	44.0
History of Premature rupture of membrane*		11	22.0
Total		**50**	**100.0**

*Time lapsed on membrane rupture from 7 hours to 10 days with a mean of 4.0 ± 3.8 days
VLBW: very low birth weight, LBW: low birth weight

Table 2. Clinical finding of studied premature neonates

Clinical Findings	No.	%
Dyspnea/Grunting	46	92.0
Tachypnea	41	82.0
Skin sclerema	5	10.0
Cyanosis	3	6.0
Poor Feeding/Lethargy	3	6.0
Coffee ground vomiting	3	6.0
Hypothermia	2	4.0
Fit	1	2.0
Irritability	1	2.0
Bilious vomiting	1	2.0
Total	**50**	**100.0**

Table 3. Laboratory findings of studied premature neonates

Variable		No.	%
CRP	Positive at birth	4	8.0
	Positive at 72 h	12	24.0
	Rising titter	32	64.0
WBC Count	Normal	40	80.0
	Leukocytosis	3	6.0
	Leukopenia	7	14.0
Neutrophils	Normal	40	80.0
	Neutrophilia	1	2.0
	Neutropenia	9	18.0
Lymphocytes	Normal	18	36.0
	Lymphocytosis	20	40.0
	Lymphocytopenia	12	24.0
Platelets	Normal Count	39	78.0
	Thrombocytopenia	11	22.0
Blood Culture (positive)	S. epidermides	4	8.0
	S. aureus	3	6.0
	Acinetobacter spp.	3	6.0
	S. Saprophyticus	2	4.0
	Gram neg. bacteria	2	4.0
	Pseudomonas Spp.	1	2.0
Total		**50**	**100.0**

Table 4. Distribution of studied children according to presence of sepsis and to results of CRP testing

CRP Testing		Confirmed Sepsis		Suspected Sepsis		No Sepsis	
		No.	%	No.	%	No.	%
CRP day 1	Positive	3	75.0	1	25.0	0	0.0
	Negative	12	26.1	28	60.9	6	13.0
CRP day 3	Positive	4	33.3	8	66.7	0	0.0
	Negative	11	28.9	21	55.3	6	15.8
Rising Titer	Yes	6	18.8	22	68.8	4	12.5
	No	9	50.0	7	38.9	2	11.1
Total		**15**	**30.0**	**29**	**58.0**	**6**	**12.0**

Table 5. Studied premature neonates according to status of blood culture and to presence of rising CRP titer Distribution (A) Screening indicators

Variable		Blood Culture			
		Positive		Negative	
		No.	%	No.	%
Raising CRP Titer	Yes	11	73.3	21	60.0
	No	4	26.7	14	40.0
Child sex	Male	10	66.7	18	51.4
	Female	5	33.3	17	48.6
Birth Weight	VLBW	8	53.3	19	54.3
	LBW	7	46.7	16	45.7
Gestational age	Very Preterm	9	60.0	21	60.0
	Late Preterm	6	40.0	14	40.0
S. epidermides		4	26.7	-	-
S. aureus		3	20.0	-	-
Acinetobacter spp.		3	20.0	-	-
S. Saprophyticus		2	13.3	-	-
Gram neg. bacteria		2	13.3	-	-
Pseudomonas Spp.		1	6.7	-	-
Clinical features	Respiratory Difficulties	11	73.3	-	-
	Lethargy and poor feeding	3	20.0	-	-
	Hypothermia	1	6.7	-	-
Outcome	Oxyhood	7	46.7	-	-
	NCPAP	6	40.0	-	-
	Ventilator	2	13.3	-	-
Total		**15**	**30.0**	**35**	**70.0**

Table 5. Studied premature neonates according to status of blood culture and to presence of rising CRP titer Distribution (B) Screening indicators

Screening Indicator	Estimate	95% CI	
		Lower	Upper
Prevalence	0.30	0.18	0.45
Sensitivity	0.73	0.45	0.91
Specificity	0.40	0.24	0.58
Accuracy	0.50	0.36	0.64
Predictive value of positive result	0.34	0.19	0.53
Predictive value of negative result	0.78	0.52	0.93

4. DISCUSSION

Over the past few decades, significant progress in the field of newborn intensive care has resulted in a remarkable reduction in both mortality and morbidity among neonates. Nevertheless, instances of infection during the postnatal period continue to be grave and have the potential to endanger lives, particularly in extremely preterm children, with fatality rates reaching as high as 50%. The clinical presentation of newborn sepsis may closely resemble that of noninfectious diseases, such as respiratory distress syndrome. Consequently, prompt and accurate identification is of utmost importance in order to mitigate potential negative outcomes for the infant. The present approach of initiating empirical antibiotic treatment in infants exhibiting signs resembling infectious diseases leads to their exposure to detrimental medication effects, complications, and the development of resistance strains (15,16). Sepsis was confirmed in 30% of our patients (15 cases) based on positive blood culture and this close to the findings of Shirazi H. et al. (17) who showed culture positive sepsis in 35% , while our finding was lower than that reported by Younis S (18) who confirmed neonatal sepsis with positive blood culture in 64.4%. Mehrotra (19) showed positive culture sepsis in 62% and Ahmed E et al (19) showed positive culture sepsis in 75.5%. According to the results of blood C&S in our study the most common organism is S. epidermides 26.7% , S. aureus and acinetobacter spp each of the last two organism show 20%, while s. saprophyticus and gram neg. bacteria each of them show 13.3% and

pseudomonas the least common organism 6.7%, which is going with Karthikeyan G and Premkumar K. (20) which show S. aureus was the predominant pathogen accounting for 61.5% of cases, also Ahmed I et al (21) showed the most common organism isolated from blood C&S was S. epidermides 15%, while the following studies against our results Mahmood A et al (22) show the most common organism was klebsiella 39.41% then followed by E. coli 11.17% also Mehrotra G. (19) show the most common organism was klebsiella 26.6% then followed by E. coli 20%, while Ahmed E et al (19) reported that the most common organism was E. coli 24.5% then followed by klebsiella 22.5%, this variation may result from criteria of studied group, sample size, or technical limitation in obtaining sample for blood culture.

The incidence of neonatal sepsis is more in male than female, it is proposed to be due to genetic origin of the sex different in vulnerability to infection. The special source of vulnerability open to females by virtue of her possession of to 'X'-chromosomes in contrast to the single 'X' of the male (19) . This can attributed to the differences in endocrine–immune interactions, specifically because of androgens in males (which reduce immunocompetence) and estrogens in females (22). In this study 66.7% of confirmed sepsis were males, and 33.3 % were females and this is similar to Klein's study (23)in which 58% of confirmed sepsis were among males and 42% in females, in study Mehrotra G (19) showed that 62% of the confirmed sepsis were males, while 38% were females, in study Getabelew A. et al (24) which show 58.2% of confirmed sepsis were male and 41.8% were female, and this against to Ashraf MN (6) which show 48.8% of confirmed sepsis were male while 51.2% were females. As per study done by Swarnkar K. and Swarnkar M. (25) show VLBW infants are at the highest risk for early neonatal sepsis than LBW, which show 87.5% and 36% respectively. This is caused, in part by an immature inexperienced immune system; a fragile cutaneous barrier; and the period of hospital stay with increased exposure to the neonatal intensive care unit (NICU) environment, including various invasive devices and procedures (19). The idea is close to our current study in which the incidence of early neonatal sepsis is more in neonates weighing less than 1500 g which show 53.3%, while those weighing from 1500-2500 g show 46.7%. It is because of lung immaturity and lack specific and non-specific antibodies in the preterm neonates, and this against to Getabelew A. et al (24) which show early onset sepsis in preterm weighing < 2500 g was 10.2%. The

clinical features in our patients with confirmed sepsis show the most common was respiratory difficulties (dyspnea, grunting with or without tachypnea) 73.3%, lethargy and poor feeding 20% and hypothermia was 6.7% which is going with Nawshad A.S.M et al (26), which show patients with confirmed EOS had respiratory difficulties 75%, lethargy 33.3%, hypothermia 25%, and this against Ahmed I et al (21) which show poor feeding which was the most common 57%, lethargy 50%, while respiratory difficulties only 25%, also Mehrotra G.(19) show lethargy 72%, respiratory difficulties 40% and hypothermia 14%. Regarding outcome of our patients with confirmed EOS 46.7% were on oxyhood, 40% where on NCPAP, while only 13.3% on ventilator which is against (24) which show 27% on NCPAP, 23.4% on ventilator and only 6.6% on oxyhood. Regarding CRP in our study sensitivity was 73%, specificity was 40% and this is going with Hisamuddin E et al (27) which show sensitivity 76.92% , while specificity 48.94% , Ahmad I et al (21) show sensitivity 67% , while specificity 19% and Sonawane VB et al (27) show 84.21% , 28.57% sensitivity and specificity respectively. Our results going against Younis S et al (18) which show sensitivity 97.3% and specificity 95.2% and Ahmed E et al (28) show 98.03%, 91% sensitivity and specificity respectively. Regarding positive predictive value (PPV) of CRP in our study show 34%, negative predictive value (NPV) of CRP show 78% , while accuracy show 50% and this is close to Sonawane VB et al. (29) which show PPV was 51.61% , NPP was 66.67% , while accuracy was 55% , also Mehrotra G (19) show NPP was 72%, and these results against to Mahmood A et al (22) which show PPV was 67.74% and NPP was 48.27% , Younis S et al show PPV was 97.3% and NPP was 95.2% and Ahmed E et al (28) show 97%, 93.7% PPV and NPP respectively. This discrepancy in observed results may be attributed to different methods of CRP estimation, difference in titer of positivity (cut off value) between laboratories or number, method and timing of sample collection. Regarding combined test results, sensitivity of CRP increased while specificity decreased. CRP was positive at birth in 4 cases out of 50 patients ;became positive in 12 cases out of 50 patients at 72 h after admission, while increasing titer in 32 patients out of 50 patients, this means no single test alone was sufficiently reliable as an indicator of infection to be a satisfactory screening tool for early onset sepsis which is similar to suggestion by Gerland SM et al (30). The presence of leucopenia, neutropenia and thrombocytopenia are poor screening tools for neonatal sepsis

and their absence is not strong evidence against neonatal sepsis. However when present, they are strong pointers to presence of sepsis (17).

5. CONCLUSIONS

CRP estimation does have a role in the diagnosis of early neonatal sepsis in preterm but the test is not specific enough to be relied upon as the only indicator. The sensitivity, specificity, positive and negative predictive values with accuracy as calculated in this study were not high enough to make it a good screening test.

Considering the high morbidity and mortality associated with EOS, clinical criteria along with other hematological parameters and diagnostic markers along with serial CRP should be considered in evaluating a neonate for EOS.

There is no significant correlation between the positivity or even rising titer of CRP and positive blood culture.

Isolation of organism from blood C&S is the gold standard for diagnosis.

Ethical Approval:

All ethical issues were approved by the author. Data collection and patients enrollment were in accordance with Declaration of Helsinki of World Medical Association , 2013 for the ethical principles of researches involving human. Signed informed consent was obtained from each participant and data were kept confidentially.

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Citation:

Abdulhadi H.H, Mohammed R.A, Jasim A.M, Al-Awqat T.A.J C-Reactive Protein as an Indicator in Early Neonatal Sepsis in Preterm. AJMS 2023; 9 (3):219-33. ***DOI: 10.5281/zenodo.8352392***