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CORRELATION OF C-REACTIVE PROTEIN AND LEUCOPENIA WITH CULTURE POSITIVE NEONATAL SEPSIS: A HOSPITAL BASED CASE CONTROL OBSERVATIONAL STUDY

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Abstract: **BACKGROUND:** Neonatal sepsis is the leading cause of newborn mortality and morbidity worldwide. To combat the problem it should be diagnosed promptly and treated adequately.

OBJECTIVES: to look for the correlation of C reactive protein and leucopenia in blood culture proven sepsis cases and culture negative suspected sepsis babies

METHOD: The study was conducted in one of the busiest hospitals of Jorhat, Assam. It is a hospital based case-control observational study. Cases were neonates with bacterial blood culture positive and controls were gestational age matched babies with suspected sepsis having negative blood culture. CRP, total count reports were studied. Data was analysed statistically using SPSS.16

RESULTS: Total 602 blood cultures were sent during the study period out of which 46(7.6%) were bacterial culture positive[29 (63%) were males and 17 (37%) were females]. Early Onset sepsis were 27(59%) and 19 (41%) were Late onset sepsis were 19 (41%). CRP(p=0.005) and leucopenia(p=0.036) had significant correlation with culture positive sepsis. Sensitivity, specificity, positive predictive value and negative predictive value of CRP was 74%, 54% , 61% and 68% respectively and that of leucopenia was 9%,100% , 100% and 53% respectively. Mean CRP was 11.28 mg/dl and mean white-cell count was 12,175/mm³ in culture positive sepsis.

CONCLUSION: CRP and leucopenia has significant correlation with culture positive sepsis. Leucopenia was associated with less number of culture positive cases but its specificity and positive predictive value were very high. Leucopenia was associated more with early onset sepsis. These diagnostic markers can be used in early diagnosis of neonatal sepsis and can help in deciding the use of antibiotics in suspected cases and in high risk cases. However, clinical diagnosis of sepsis is also very important and should always be considered in deciding the management of neonatal sepsis.

Index Terms **- C-Reactive protein, Leucopenia, Neonatal-sepsis, early onset sepsis, late onset sepsis**

I.INTRODUCTION:

Neonatal Sepsis is infection in newborn babies within first 28 days of life and specially refers to presence of bacterial blood stream infection (such as pneumonia, meningitis, pyelonephritis or gastroenteritis) [1]. Neonatal sepsis is the leading cause of newborn mortality and morbidity worldwide. Early Onset neonatal sepsis is sepsis occurring within first 72 hours of life and Late Onset Neonatal Sepsis is sepsis occurring beyond first 72 hours of life[1].Neonatal sepsis is the most common cause of newborn death in hospital as well as in community in developing countries[1]. To control the neonatal mortality and morbidity neonatal sepsis should be identified at the earliest and treated appropriately with judicious use of antibiotics. Gold standard for diagnosing neonatal sepsis is blood culture but the results take 48 to 72 hours and sometimes even longer[2]. This may result in delaying of treatment. So certain rapidly diagnosing tests such as C reactive protein, total white cell count, absolute neutrophil count, micro ESR, immature to mature neutrophil count ratio, etc collectively known as sepsis screen can be used[3]. Low values of white cell count are associated with early onset sepsis[4] and higher or lower white blood cell count are associated with late onset sepsis[5]. Since neonatal sepsis is a leading cause of neonatal mortality, doctors are often bound to administer antibiotics in babies with risk factors for sepsis and in sepsis suspected babies. Unfortunately, both broad spectrum antibiotics and prolonged use of empirical antibiotics may adversely affect the babies and increase the threat of antimicrobial resistance

globally[6]. In this study we have tried to find out the correlation of CRP and total count with blood culture positive sepsis cases so that antibiotic stewardship could be practiced. Studies have been done in the past to see their association but more studies are required to understand their association accurately so that neonatal sepsis is diagnosed and treated promptly with judicious use of antibiotics.

II.AIMS AND OBJECTIVES:

Primary objectives:

1/ to look for the correlation of C reactive protein in blood culture proven sepsis cases and culture negative suspected sepsis cases

2/ to look for the correlation of total white blood cell count in blood culture proven sepsis cases and culture negative suspected sepsis cases

Secondary objectives:

1/ to look for the values of CRP and total count in culture proven sepsis

2/ to look for the distribution of CRP and total count less than 5000/mm³ in early and late onset sepsis

MATERIALS AND METHOD:

Place of Study: the study was conducted in Sanjivani Hospital, Jorhat, one of the busiest hospitals of Jorhat, Assam

Study Design: Hospital based case-control observational study

Duration of Study : 18 months (May 2019 – October 2020)

Method of study: It was a cross sectional study conducted on the admitted patients with suspicion of sepsis. 1-2 ml of blood was drawn prior to starting antimicrobial treatment maintaining strict aseptic and antiseptic precautions. Blood was sent and analysed in the laboratory as per standard hospital protocol. Total WBC count was sent along with blood culture and CRP was sent after 12 hours of birth in patients with risk factors of early onset sepsis or after 12 hours of onset of symptoms in sepsis suspected cases. Quality assurance was strictly adhered to. Management of the neonates was done according to standard Neonatal Intensive Care Unit (NICU) protocol. Blood culture reports of all patients were traced from the hospital laboratory data. Institutional ethics committee clearance was obtained.

Cases and control are defined as

Cases- Neonates with bacterial blood culture positive

Controls- Gestational age matched neonates with suspected sepsis having negative blood culture

Exclusion criteria:

1/ Fungal sepsis were excluded

2/ Babies with COVID-19 positive mothers

3/ Contaminants were excluded from the study.

4/ Blood culture negative babies having proven urinary tract infection, meningitis, congenital pneumonia

Variables studied included

1/ Correlation of C reactive protein in cases and controls

2/ Correlation of total white blood cell count in cases and controls

3/ Values of CRP and total count in culture proven sepsis

4/ Distribution of CRP and Total count less than 5000/mm³ in early and late onset sepsis

STATISTICAL METHODS : The data obtained was tabulated and analysed statistically using social science system version SPSS.16

III. RESULTS AND OBSERVATION:

Total 602 blood cultures were performed during the study period out of which 46(7.6%) were bacterial culture positive, out of which 29 (63%) were males and 17 (37%) were females. Among the culture positive sepsis babies 27 (59%) were Early onset sepsis and 19 (41%) were Late onset sepsis. Similar number of controls(48) were taken from the sepsis suspected babies during the same study period who turned out to be bacterial culture negative.

Table 1: Comparison of CRP and Total count in Cases and Controls

VARIABLES	SUBGROUP	CASES n =46	CONTROLS n= 48	P VALUE
CRP	Positive (>1mg/dl)	34(74%)	22(46%)	0.005
	Negative(≤1mg/dl)	12(26%)	26(54%)	
TOTAL COUNT	<5000/mm³	4(9%)	0	0.036
	>5000/mm³	42(91%)	48(100%)	

Analysis of the data showed that CRP(p=0.005) and Total count less than 5000(p=0.036) had significant correlation with culture positive sepsis. Among the culture positive sepsis 74%(34 out of 46) had CRP more than 1mg/dl and 9% (4 out of 46) had total count less than 5000 whereas among the culture negative suspected sepsis babies 46%(22 out of 48) had CRP more than 1mg/dl and no one had total count less than 5000. Sensitivity of CRP values more than 1 mg/dl in culture proven bacterial sepsis was 74%, specificity was 54%, positive predictive value was 61% and negative predictive value was 68%. Sensitivity of total WBC count less than 5000/mm³ was 9%, specificity was 100% , positive predictive value was 100% and negative predictive value was 53%.

Table 2: Values of CRP and Total Count in Culture Positive Sepsis

	MEAN	STANDARD DEVIATION	RANGE	
			MINIMUM	MAXIMUM
CRP	11.28 mg/dl	1.4 mg/dl	0.28 mg/dl	42.83 mg/dl
TOTAL COUNT	12175/mm³	5173/mm³	2200/mm³	19900/mm³

Among the culture positive sepsis babies mean CRP was 11.28 mg/dl, standard deviation was 1.4 mg/dl. Minimum value of CRP was 0.28 mg/dl and maximum value of CRP was 42.83 mg/dl. Mean value of total count among the culture positive sepsis babies was 12,175/mm³, standard deviation was 5173/mm³. Minimum value of total count was 2200/mm³ and maximum value was 19,900/mm³.

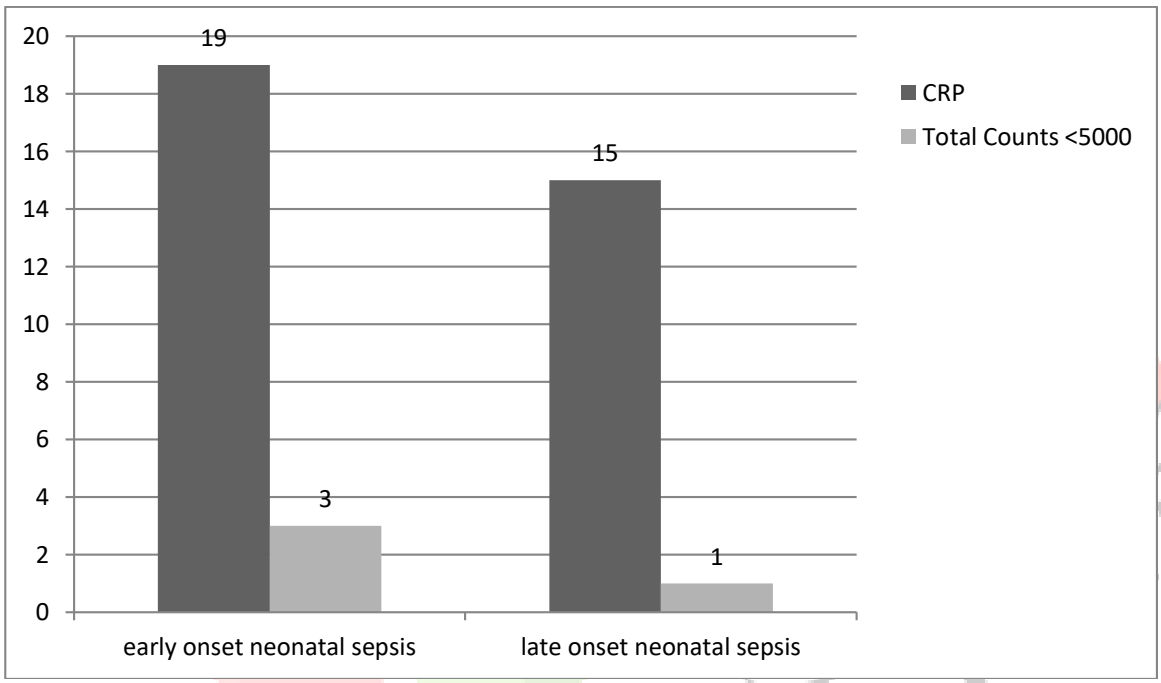

Figure 1: Distribution of CRP and Total count in Early and Late onset Neonatal Sepsis

Results showed that 70%(19 out of 27) of the Early onset culture proven sepsis cases and 79%(15 out of 19) of the late onset culture proven sepsis cases had CRP values more than 1mg/dl. And 11%(3 out of 27) of the early onset culture proven sepsis cases and 5%(1 out of 19) of the late onset culture proven sepsis cases had total count less than 5000/mm³.

IV.DISCUSSION :

In this study we have tried to find out the correlation of C reactive protein and total white blood cell count with culture positive neonatal sepsis . We have found that total 602 blood cultures were performed during the study period out of which 46 were bacterial culture positive. The incidence of culture positive bacterial sepsis among sepsis suspected babies was 7.6%. S Thapa et al in their study have found the incidence of significant bacterial growth to be 10.8% [7]

Among the bacterial sepsis positive babies 29 (63%) were males and 17 (37%) were females. Male : Female ratio in our study was 1.8:1. Previous studies have also found that there is slightly higher incidence of sepsis among males. Male female ratio in their study was found to be 1.38:1 [8]. 27(59%) cases were early onset sepsis and 19 (41%) were late onset sepsis. Prevalence of early onset sepsis was greater than late onset sepsis. S Thapa et al in their study also found the prevalence of early onset sepsis(62.5%) to be higher than late onset sepsis(37.5%) [7]

C reactive protein(CRP) is a protein produced by the liver. It increases in blood in response to inflammation due to injury or infection.[9]. It increases in blood after 8 to 10 hours following inflammation. CRP more than 1 mg/dl is a marker of neonatal sepsis[10]. CRP concentration increases physiologically in neonates within the first few days of birth and also in some other conditions like birth asphyxia and meconium aspiration[10][11]. In our study we found that CRP(p=0.005) had significant correlation with culture positive sepsis. Among the culture positive sepsis 74%(34 out of 46) had CRP more than 1mg/dl whereas, among the culture negative suspected sepsis babies 46%(22 out of 48) had CRP more than 1mg/dl .Sensitivity of CRP

values more than 1 mg/dl in culture proven bacterial sepsis was 74%, specificity was 54%, positive predictive value was 61% and negative predictive value was 68%. HR Hassan et al in their study found the sensitivity of CRP in neonatal sepsis to be 95.2% and negative predictive value to be 89.3% [10], w hile, E Hisamuddin et al in their study had found the sensitivity and specificity of CRP in the diagnosis of neonatal sepsis to be 76.92% and 53.49% respectively which was similar to our study .The positive predictive value was found to be 80% and the negative predictive value was found to be 48.94% [11].

In our study leucopenia, that is, total WBC count <5000/mm^3 is taken as a diagnostic criteria of neonatal sepsis. Total WBC count less than 5000(p=0.036) had significant correlation with culture positive sepsis. Among the culture positive sepsis 9% (4 out of 46) had total count less than 5000 whereas among the culture negative suspected sepsis babies no one had total count less than 5000. Sensitivity of total WBC count less than 5000/mm^3 was 9%, specificity was 100% , positive predictive value was 100% and negative predictive value was 53%. Previous studies have shown leucopenia to be a better predictor of septicaemia as compared to leucocytosis(Specificity 87.5% vs 25%)[13]. Very severe and fatal bacterial sepsis are often associated with leucopenia[14]. We found that leucopenia was associated with less number of culture positive cases but it had significant correlation with culture positive bacterial sepsis and its specificity and positive predictive value were very high.

Among the culture positive sepsis babies mean CRP was 11.28 mg/dl in our study, standard deviation was 1.4 mg/dl. The minimum value of CRP was 0.28 mg/dl and maximum value of CRP was 42.83 mg/dl. Previous studies have found mean CRP response in term and near term babies was 10ml/dl[15]. Mean value of total count among the culture positive sepsis babies was 12,175/mm^3, standard deviation was 5,173/mm^3. The minimum value of total count was 2,200/mm^3 and maximum value was 19,900/mm^3.

We found that 70%(19 out of 27) of the early onset culture proven sepsis cases and 79%(15 out of 19) of the late onset culture proven sepsis cases had CRP values more than 1mg/dl . And 11%(3 out of 27) of the early onset culture proven sepsis cases and 5%(1 out of 19) of the late onset culture proven sepsis cases had total count less than 5000/mm^3.Studies have shown that leucopenia is associated with early onset sepsis[4] and leucocytosis or leucopenia is associated with late onset sepsis [5].This is consistent with the findings in our study.

Neonatal sepsis is an important cause of neonatal mortality and morbidity worldwide. So a collective effort should be made to combat this problem. Doctors are often bound to administer antibiotics in babies with risk factors for sepsis and in sepsis suspected babies as the blood culture report takes time to come and delay in treatment might risk their lives. On the other hand, both broad spectrum antibiotics and their prolonged use may adversely affect the babies and increase the threat of antimicrobial resistance globally[6]. In this study we have tried to find out the correlation of CRP and total count with blood culture positive sepsis cases so that sepsis can be diagnosed early and antibiotics can be used judiciously in treatment. Studies have been done in the past on CRP, total blood count and on neonatal sepsis but more studies are required to understand the correlation between these commonly available diagnostic markers with culture positive sepsis precisely so that sepsis in newborns is diagnosed and treated promptly with judicious use of antibiotics.

Our study has one limitation; we did not take serial measurements of CRP in our study. CRP usually rises 8 to 9 hours after inflammation as liver takes time to produce it and reaches peak in 24 to 48 hours following inflammation. But this was done intentionally to see the accuracy of CRP in diagnosing neonatal sepsis with a single test result. To combat this problem we measured CRP after 12 hours of birth in asymptomatic neonates with risk factors of sepsis and after 12 hours of onset of signs or symptoms in sepsis suspected babies.

V.CONCLUSION:

In this study we have tried to find out the correlation of CRP and total WBC count with blood culture positive sepsis cases so that sepsis can be diagnosed early and antibiotics can be used judiciously in correct time in the treatment of sepsis. Neonatal sepsis is one of the leading causes of neonatal mortality and morbidity worldwide. So a comprehensive effort should be made to tackle this problem timely. Gold standard for diagnosis of neonatal sepsis is blood culture but it takes 48 to 72 hours for the report and delay in treatment may significantly affect the health of the neonates. We found that CRP and leucopenia has significant correlation with culture positive sepsis. Leucopenia was associated with less number of culture positive cases but its specificity and positive predictive value were very high. Leucopenia was associated more commonly with early onset sepsis. These diagnostic markers can be used in early diagnosis of neonatal sepsis and can help in deciding the use of antibiotics in suspected cases and in high risk cases. However, clinical diagnosis of sepsis is also very important and should always be considered in deciding the management of neonatal sepsis.

VI. REFERENCE:

1/Neonatal sepsis [Internet]. En.wikipedia.org. 2020 [cited 17 November 2020]. Available from: https://en.wikipedia.org/wiki/Neonatal_sepsis

2/ Healthlibrary.osfhealthcare.org. 2020. *Blood Culture*. [online] Available at: <http://healthlibrary.osfhealthcare.org/library/TestsProcedures/167,blood_culture> [Accessed 25 November 2020].

3/ Paul VK, Singh M. Diagnosis and treatment of neonatal sepsis. Indian Pediatr 1986;23:1023-35. [PUBMED]

4/ Hornik CP, Benjamin DK, Becker KC, et al. Use of the complete blood cell count in early-onset neonatal sepsis. Pediatr Infect Dis J 2012;31:799–802. [PMC free article] [PubMed] [Google Scholar]

5/Hornik CP, Benjamin DK, Becker KC, et al. Use of the complete blood cell count in late-onset neonatal sepsis. Pediatr Infect Dis J 2012;31:803–7. [PMC free article] [PubMed] [Google Scholar]

6/ Zea-Vera, A. and Ochoa, T., 2015. Challenges in the diagnosis and management of neonatal sepsis. *Journal of Tropical Pediatrics*, 61(1), pp.1-13.

7/ Thapa S, Sapkota L. Changing Trend of Neonatal Septicemia and Antibiotic Susceptibility Pattern of Isolates in Nepal. International Journal of Pediatrics. 2019;2019:1-7.

8/Vasantha AR, Kutty SN, Joseph Theodore RB. Neonatal sepsis: Aetiological agents and risk factors. J AcadClinMicrobiol [serial online] 2017 [cited 2020 Nov 17];19:36-41. Available from: https://www.jacmjournal.org/text.asp?2017/19/1/36/208071

9/ Tests, M., 2020. *C-Reactive Protein (CRP) Test: Medlineplus Medical Test*. [online] Medlineplus.gov. Available at: <https://medlineplus.gov/lab-tests/c-reactive-protein-crp-test/> [Accessed 26 November 2020].

10/ Hassan HR, Gohil JR, Desai R, Mehta RR, Chaudhary VP. Correlation of blood culture results with the sepsis score and sepsis screen in the diagnosis of early-onset neonatal septicemia. J Clin Neonatol [serial online] 2016 [cited 2020 Nov 26];5:193-8. Available from: https://www.jcnonweb.com/text.asp?2016/5/3/193/191263

11/ Kawamura M, Nishida H. Th e usefulness of serial C-reactive protein measurement in managing neonatal infection. Acta Paediatr 1995;84:10-3. [PUBMED]

12/ Hisamuddin E, Hisam A, Wahid S, Raza G. Validity of C-reactive protein (CRP) for diagnosis of neonatal sepsis. *Pak J Med Sci*. 2015;31(3):527-531. doi:10.12669/pjms.313.6668

13/ Misra RN, Jadhav SV, Ghosh P, Gandham N, Angadi K, Vyawahare C. Role of sepsis screen in the diagnosis of neonatal sepsis. Med J DY Patil Univ [serial online] 2013 [cited 2020 Nov 26];6:254-7. Available from: https://www.mjdrdypu.org/text.asp?2013/6/3/254/114649

14/ Stoll BJ. The global impact of neonatal infection. Clin Perinatol 1997;24:1-21 [PUBMED]

15/ Vasiljević B, Antonović O, Maglajlić-Djukić S, Gojnić M. [The serum level of C-reactive protein in neonatal sepsis]. Srp Arh Celok Lek. 2008 May-Jun;136(5-6):253-7. Serbian. doi: 10.2298/sarh0806253v. PMID: 18792621