www.jmscr.igmpublication.org
Impact Factor (SJIF): 6.379
Index Copernicus Value: 79.54
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossrefDOI: https://dx.doi.org/10.18535/jmscr/v6i11.30

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Study to Evaluate the Role of High Sensitivity – C Reactive Protein (hsCRP) in the early Diagnosis of Neonatal Sepsis

Authors
Dr M.Muralidharan[1], Dr S.Ramesh[2], Dr S. Saravanan[3*], Dr S. Chidambaranathan[4], Dr Praveenkumar[5]
[1]Post Graduate, Department of Paeditrics, RMMCH, Chidambaram-608002, Tamilnadu, India
[2]Professor and Head, Department of Paeditrics, RMMCH, Chidambaram-608002, Tamilnadu, India
[3,4]Associate Professor, Department of Paeditrics, RMMCH, Chidambaram-608002, Tamilnadu, India
[5]Lecturer, Department of Paeditrics, RMMCH, Chidambaram-608002, Tamilnadu, India
Corresponding Author
Dr. S. Saravanan
Associate Professor, Department of Paeditrics, RMMCH, Chidambaram-608002, Tamilnadu, India
Email: *paedssaravanan@gmail.com*

Abstract
Background: *Neonatal sepsis is a clinical syndrome of bacteremia characterized by systemic signs and symptoms of infection in the first month of life. Neonatal sepsis encompass systemic infection of the newborn including septicemia, meningitis, pneumonia, arthritis, osteomyelitis and urinary tract infection of the newborn[1]. The contribution of neonatal sepsis to high morbidity and mortality rate makes it an important subject for research so as to find out the possible solution. Prompt diagnosis of neonatal sepsis is of paramount importance. As there is no rapid and reliable test yet for the diagnosis of neonatal sepsis, serial HS-CRP measurement can be used for its early detection as well as exclusion of infection in the neonates.*
Methodology: *The current study is a prospective study conducted among 150 neonates admitted in the department of Paediatrics, Rajah Muthiah Medical College and Hospital, Chidambaram with clinical suspicion of sepsis by purposive sampling technique from October 2016 to October 2018. Detailed history and venous blood samples were collected from all neonates, clinical and laboratory parameters were recorded and analysed.*
Results: *The qualitative CRP levels with a cut off value greater than 6.0mg/l showed a sensitivity of 69.74% and specificity of 71.62% with a diagnostic accuracy of 70.67%. The HSCRP-1 collected within 12 hours of onset of symptoms with a cut of value ≥3mg/lt showed a sensitivity of 93.42% and specificity of 91.89% with a diagnostic accuracy of 92.67%. HSCRP-2 collected 24 hours later with a cut of value ≥3mg/lt showed a sensitivity of 98.68% and specificity of 93.24% with increased diagnostic accuracy of 96.0%.*
Conclusion: *Serial measurement of High Sensitivity CRP measured quantitatively is more sensitive and specific in diagnosing neonatal sepsis with increased diagnostic accuracy and found to be more superior to conventional method of measuring CRP qualitatively.*
Keywords: *Neonatal Sepsis, CRP, HSCRP, Culture Positive Sepsis*.

Introduction

Many of the manifestations of the neonatal sepsis have their counterparts in non-infectious neonatal disorder.[2] Thus the inability to be certain of infection coupled with non-specific signs of life threatening illness in neonates have resulted in widespread use of antibiotics aggravating the problem of antibiotic resistance.[3]

Neonatal sepsis is categorized into early onset sepsis, occurring within 72 hrs of life and late onset sepsis, occurring after 72 hrs of life.

Neonates can also be categorized as having proven sepsis if bacteria are isolated in blood, CSF or urine; probable sepsis if clinical and laboratory findings are consistent with bacterial infection without positive culture; or clinical sepsis in whom only clinical features are consis-tent with sepsis, without laboratory abnormalities or growth of organism in body fluid cultures.

The diagnosis of neonatal sepsis is difficult to make solely on historical or clinical ground. Laboratory evaluation is essential in the diagnosis and confirmation of infection. There is no rapid and reliable test for confirmation of diagnosis yet. The treatment for sepsis is generally started when clinical findings are supported by indirect early markers of infection.[4]

Positive culture of blood, CSF or urine are the gold standard for confirming sepsis, however in considerable proportion of neonates at risk of infection, culture result may be influenced by previous antibiotic exposure.[1] The sole use of culture to diagnose neonatal infection has limitations as it may take 24 to 72 hrs to obtain culture reports.

The well-known laboratory parameters indicating infection include WBC count, immature to total WBC ratio (I:T ratio), ESR, CRP and procalcitonin in. Similarly in recent years, several new markers of infection have been investigated such as Tumour Necrosis Factor (TNF), Interleukin6 (IL-6), IL-1 receptor antagonist, procalcitonin in, Granulocyte Colony. Stimulating Factor (GCSF), leukocyte-∝3 proteinase inhibitor and most recently CD 116 as a cell surface marker. But these markers have not yet made the progress from the laboratory to clinical applications.

C- reactive protein is an acute phase protein belonging to pentraxin family of protein. It is exclusively produced in liver and is secreted in increased amounts within 6 hours of an acute inflammatory stimulus. The plasma level can double in every 8 hours, reaching a peak at 24-48 hours of the stimulus.[5]

After effective treatment or removal of the inflammatory stimulus, level can fall as rapidly as 5-7 hours.

CRP is present in the serum of normal person at the concentration ranging up to 6mg/l, since the protein is produced by the fetus and neonate and does not pass the placental barrier, it can be used for the early detection of neonatal sepsis.[7] The CRP level increases dramatically following the bacterial infection which may be particularly helpful for the diagnosis and monitoring of bacterial septicaemia in neonates. The concentration of CRP accurately parallels the activity of inflammatory process and the concentration decreases much faster than the any other acute phase parameter which is particularly useful in monitoring appropriate treatment of bacterial disease with antibiotics. The value of CRP is reliable in the 24-48 hrs after onset of infection.

As there is no rapid and reliable test yet for the diagnosis of neonatal sepsis, serial HS-CRP measurement can be used for its early detection as well as exclusion of infection in the neonates.[6,7]

Quantitative CRP also called as high sensitivity CRP assay can detect CRP measuring as low as 0.3mg/dl to 40 mg/ dl, making it superior to qualitative measurements of CRP.[6,7]

The concentration of many serum proteins raises in response to inflammation, associated with infection, trauma or tissue damage. Among these

proteins important being CRP, haptoglobin and fibrinogen. These can be used as non-specific indicators of bacterial sepsis.

Sepsis screen tests involving WBC indices and CRP form simple, cheap, rapid and early available parameters with reasonable diagnostic accuracy especially when they are used in combination. On this basis early and rational antibiotics therapy can be started in critical septicaemic infants.

Objectives

1. To evaluate the role of high sensitivity –c reactive protein (hsCRP) in the early diagnosis of neonatal sepsis.
2. To Compare hsCRP with CRP and blood culture in early diagnosis of neonatal sepsis.

Material and Methods

Source of Data

This is a Prospective study. Data will be collected from neonates admitted to Department of Pediatrics, RMMCH, with clinical suspicion of sepsis by purposive sampling technique.

The study was conducted from October 2016 to October 2018 and 150 neonates were included in the study.

Method of Collection of Data

Detailed antenatal history, birth events, APGAR Score, sex and weight of the babies will be recorded from all patients. Gestational age of neonate will be assessed by using new Ballard score. 3 ml venous Blood was collected from all patients under aseptic precautions and tested for

1. Serum hsCRP (Cut off value for hsCRP used in the study is 3mg/l within 12hrs of life and 3mg/l for 12 hrs and later samples.[13])
2. CRP levels with a cut off value of > 6mg/l
3. Septic screen.
   Total count.
   Absolute neutrophil count.
   I/T ratio.
   ESR.
   Platelet count.
4. Blood culture or urine culture or cerebrospinal fluid (CSF) culture.

Based on the laboratory findings, neonates will be divided into 3 groups

a) No sepsis (hsCRP negative, septic screen negative, culture negative)
b) Probable sepsis (hsCRP positive or septic screen positive)
c) Culture proven sepsis.

Inclusion Criteria

1. Neonates born to mothers with atleast 3 of the following risk factors are included.[14,15,]

a) Premature rupture of membrane for more than 18 hours.
b) Single unclean or more than 3 sterile vaginal examinations after rupture of membrane.
c) History of maternal fever within 2 weeks of delivery.
d) Foul smelling liquor *and/or me conium.
e) History of untreated / partially treated maternal urinary tract infection.
f) Prolonged labour. (Sum of first and second stage of labour > 24 hrs).
g) Perinatal asphyxia (APGAR score<4 at 1 min).
h) Low birth weight.

*Single criteria enough for considering diagnosis of probable sepsis.[14]

2. Neonates admitted in neonatal intensive care unit with provisional diagnosis of sepsis.

As per Integrated Management of Neonatal and Childhood Illness (IMNCI) guidelines-

a. convulsions or,
b. fast breathing (60 breaths per minute or more) or,
c. severe chest indrawing or nasal flaring or grunting or,
d. bulging fontanelle or,
e. 10 or more skin pustules or big boil or,

f. axillary temperature 37.5 ^{0} C or above, or less than 35.5^{0} C or,
g. lethargic or unconscious or,
h. less than normal movements.

Exclusion Criteria

1. Neonates less than 28 weeks.
2. Neonates with weight less than 1000 grams.
3. Neonates with suspected TORCH group of infection.

Results

Fig.1: Distribution of sex in study population

In the present study female babies higher proportion were culture positive than the male babies. In culture negative sepsis again female babies were in higher percentage.

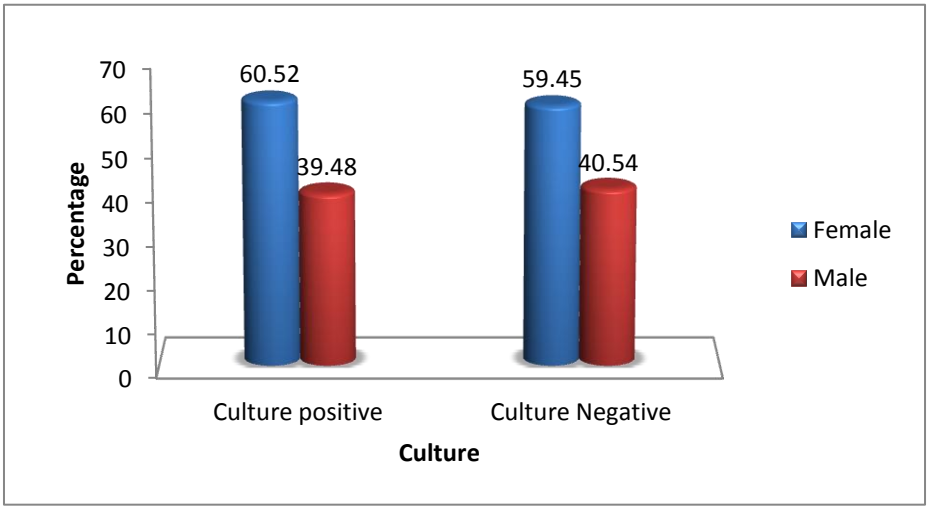


Fig.2: Distribution of proven sepsis based on gestational age

In the present study maximum percentage of culture positivity was in the age group of 32-34 weeks and least positivity shown in the age group of 28-30 weeks of gestational age.

In culture negative sepsis maximum percentage falls in 37 and above gestational age. P value not significant

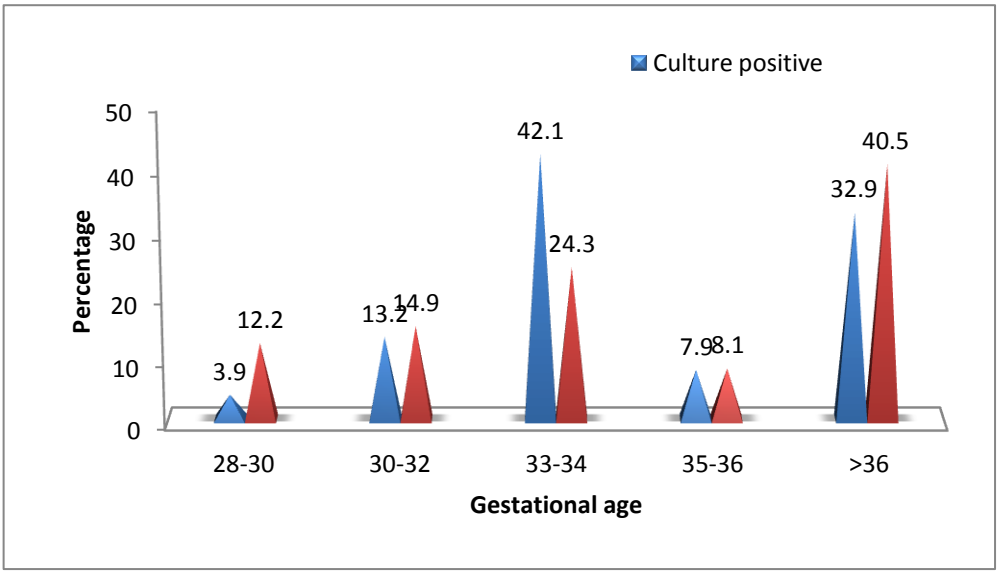


FIG.3: Shows distribution of culture positive in sepsis

In the present study population the early onset sepsis is maximally detected by culture sensitivity comprising 63.2% and the late onset sepsis is minimally detected by culture positivity comprising 36.8%.when comes to culture negative sepsis the early onset sepsis is detected less with 59.5%. Late onset sepsis with 40.5%.

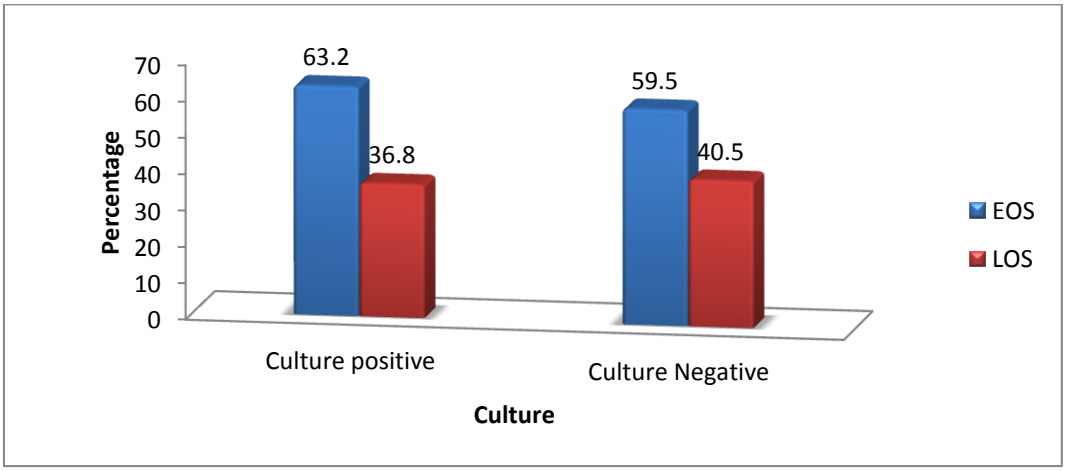


Fig.4: Shows distribution of perinatal risk factors among neonates with early onset sepsis

Among the risk factors low birth weight and preterm babies having EOS had significant percentage variation between culture positivity and negativity with culture positive in 81.2% and negativity in 61.5%. The risk factor PROM was detected the most by culture positivity.. The risk factors foul smelling liquor and maternal fever detects sepsis by culture positivity minimally.

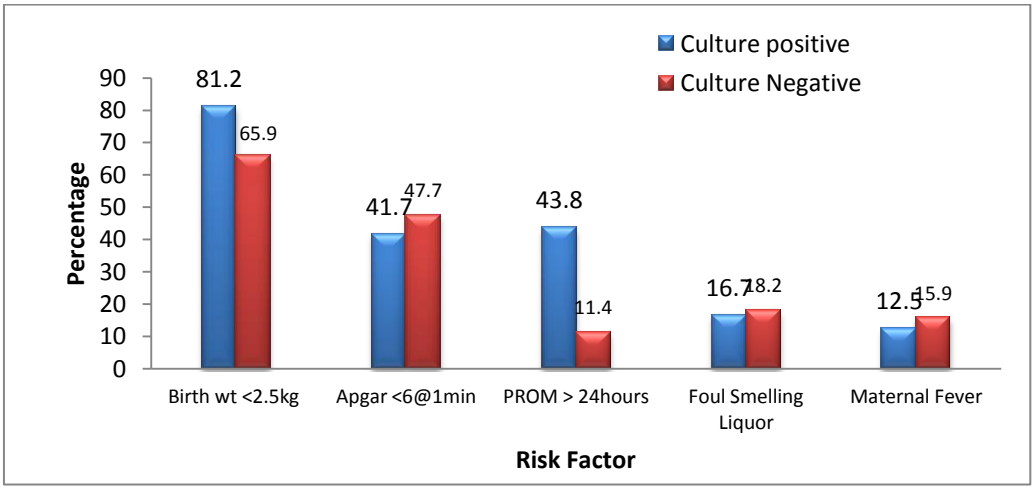


Table 1: Distribution of CRP Values among Sepsis (Both Culture Negative and Culture Positive)

Diagnosis	CRP # 1 in mg/dl		HSCRP #1 in mg/dl		HSCRP # 2 in mg/dl	
	Mean	SD	Mean	SD	Mean	SD
Culture Positive (n = 76)	6.52	3.37	4.13	0.66	9.29	1.78
Culture Negative (n = 74)	3.79	2.26	2.17	0.911	2.30	0.84
F value	33.619		226.249		932.714	
P value	0.000		0.000		0.000	

In all culture negative group of babies the mean CRP, hs-CRP1, hs-CRP2 value is significantly lower than the mean value of culture positive group. However the mean and standard deviation value of hscrp2 shows higher probability in detecting sepsis.

Fig.5: First C-Reactive Protein (Crp # 1) Results in Culture Negative and Culture Positive Sepsis

The first CRP in culture positive sepsis had a sensitivity of 69% and specificity of 71%, with a positive predictive value of 71.62% and negative predictive value of 69.7%.

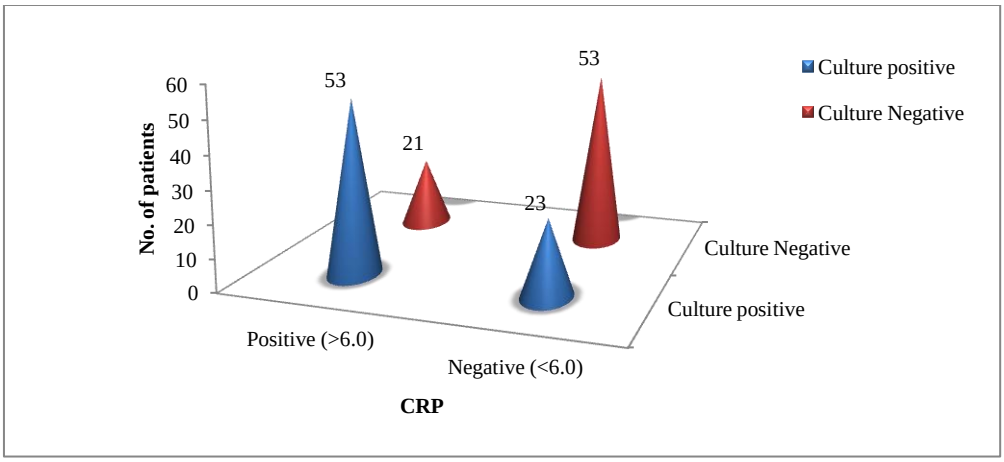


Fig.6: First High Sensitive C-Reactive Protein (HsCRP # 1) Results in Culture Negative and Culture Positive Sepsis

The HSCRP1 in culture positive sepsis had a sensitivity of 93.42% and specificity of 91.89%, with a positive predictive value of 92.21% and negative predictive value of 93.15% and accuracy of 92.67%.

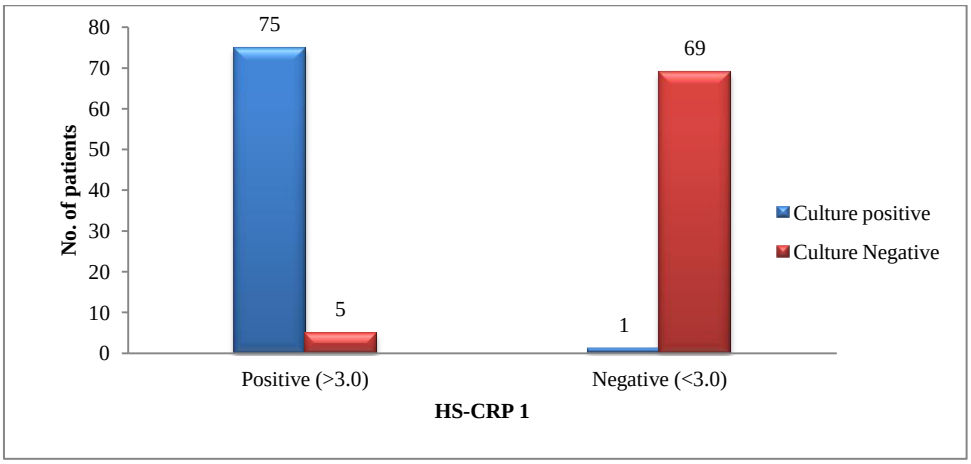
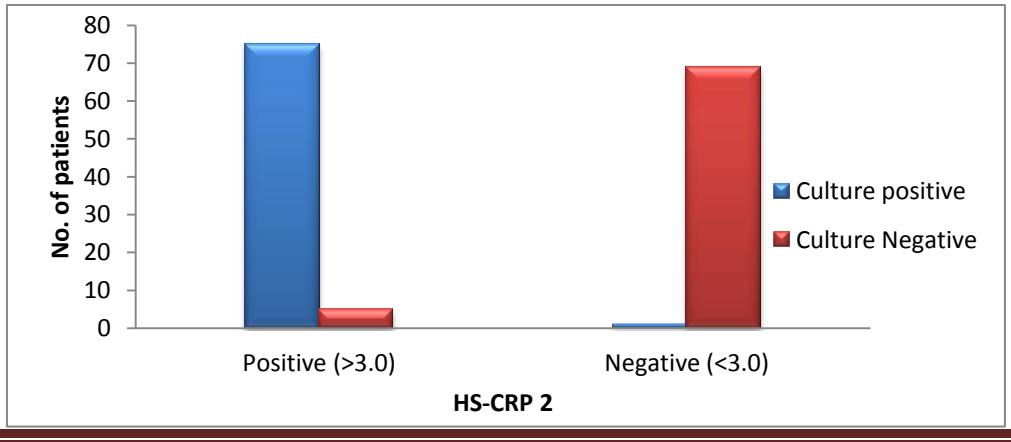


Fig.7: Second High Sensitive C-Reactive Protein (HsCRP # 2) Results in Culture Negative And Culture Positive Sepsis

The HSCRP2 in culture positive sepsis had a sensitivity of 98.62 % and specificity of 93.24%, with a positive predictive value of 93.75% and negative predictive value of 98.57% and accuracy of 96.00 %.



Discussion

In the present study an attempt has been made to know the various etiological agents responsible for neonatal septicemia and correlate the efficacy of the HSCRP, CRP and blood culture parameters. In this section we compare the results of our study with the studies done by different authors. Maximum culture positive cases were seen in neonates <3 days old (early onset septicemia) as compared to neonates aged > 3 days (late onset septicemia) in the present study. Similar observations were seen in the studies done by Varsha et al[8] and National Neonatal and Perinatal Data base[13] who also reported a higher proporation of early onset septicemia cases. This could be due to ascending infection following rupture of membranes or during the passage of the baby through the infected birth canal or at the time of resuscitation in the labour room. The higher proportion of EOS cases may be due to the immature immunological responses of the neonates in the 1st week of life, making them more susceptible to infections in this period.

The present study clearly shows a higher proportion of cases having Birth Asphyxia, prolonged rupture of membranes for > 24 hours and prolonged labour in developing definitive septicemia. This is comparable with study conducted by Yancey et al[9] and St Geme et al[10].

It is also evident from present study that nearly an equal proportion of cases had birth weight ≤ 2.5kgs and Gestational age < 37 weeks as risk factors for developing septicemia. This is comparable with study conducted by Dawodu et al[11], Tallur et al[11] and Roy et al[12]. The variations in the occurrence of perinatal risk factors probably reflect differences in the rates of occurrence of the predisposing risk factors in the various studies. In the present study single CRP value has negative predictive value of 69.70% which is comparable to observation made by other studies.

The difference in various studies is due to different cutoff value used in the qualitative test (kit). We had higher sensitivity because our cut-off value was 6mg/L. In the present study HSCRP1 and HSCRP2 had a higher sensitivity and specificity which is comparable to observation made by other studies, also both positive predictive value and negative predictive value were higher compared to previous studies. HSCRP2 which was taken 24 hours after the HSCRP1 had higher sensitivity and specificity overall and had higher accuracy in predicting neonatal sepsis. The difference in various studies is due to different cutoff value used in the qualitative test (kit). We had higher sensitivity because our cut-off value was 3mg/L.

Conclusion

1. Higher proportion of septic babies were females, low birth weight and preterm and most presented within 3 days of life(early onset sepsis).
2. Higher proportion of early onset septic babies had birth asphyxia and premature rupture of membranes as perinatal risk factors.
3. Serial HSCRP measurements showed very high sensitivity, specificity, high predictive values and increased diagnostic accuracy than a single HSCRP measurement and qualitative measurement of crp in conventional methods.
4. Hscrp was superior to qualitative crp in early diagnosis of neonatal sepsis and in instituting antibiotic therapy.

References

1. Rajiv Aggarwaf, Nupur Sarkar, Ashok K.Deorari, Vinod K. Paul. Sepsis in the Newborn. Indian J Pediatr 2001; 68(12): 1143 – 7.
2. Barbara J.Stoll, Infections of the Neonatal infant. In: Nelson Textbook of Pediatrics (18th Edition). Eds Behrman RE, Kleigman RM, Jenson HB. Philadelphia, WB Saunders Company,2008; pp.794-811.

3. Karen M.Puopolo, Bacterial and fungal infections. In: Cloherty JP the and Stark AR. (eds). Manual of neonatal care.6 edition; Philadelphia : Lippincott Williams and Wilkins, 2008 : PP. 274- 301.
4. Singh M. Perinatal Infections In: Care of the Newborn. 4 ed; New Delhi: Sagar publication, 1991: PP 168-171.
5. C-reactive protein. Elisa kit. In: Gewurz H, Mold C, Siegel J, Fiedel B (eds). C-reactive protein and acute phase response. Advances.
6. J David M Edgar A, Vanessa Gabriel, J Ruth Gallimore, Stanley A McMillan and Judith Grant, A prospective study of the sensitivity, specificity and diagnostic performance of soluble intercellular adhesion molecule 1, highly sensitive C-reactive protein, soluble E-selectin and serum amyloid A in the diagnosis of neonatal infection, BMC Pediatrics. 2010 10:22, 0.1186/1471-2431-10-22.
7. Purushothaman Ganesan, Priyadarshini Shanmugam, Shameem Banu Abdul Sattar and Shenbaga Lalitha Shankar, Evaluation of IL-6, CRP and Hs-CRP as early markers of neonatal sepsis, Journal of clinical and diagnostic research: JCDR 10 (5), 0013,2016.
8. Varsha. Usha Rusia, Meera Sikka, Faridi MMA, Nishi Madan, Validity of hematologic parameters in identification of early and late onset neonatal infection. Indian J Pathol Microbiol 2003; 46 (4) 565 – 8.
9. Yancy MK, Patric D, Paul K et al. Risk factors for neonatal sepsis. Obstetrics and Gyencology 1996; 87:188 -194.
10. Joseph W. St. Geme Jr. Dennis L. Murray, JoAnne Carter, Calvin J. Hobel, Rosemar D. Leake, Bascom F. Anthony et al. Perinatal bacterial infection management. J Pediatr 1984 Apr; 104 (4): 608 – 13
11. Dawodu A, Umran K, Twum – Danso K. A case study of neonatal sepsis: Experience from Saudi Pillai, J Trop Pediatrics. 1997 ; 43:84 – 88.
12. Roy I, Jain A Kumar M, Agarwal SK. Bacteriology of Neonatal Septicemia in a Tertiary care Hospital of Northern India. Indian Journal of Medical Microbiology 2002; 20(3): 156 – 9.
13. National Neonatal Database. Report 2002–03. Published by NNDP nodal center, Department of Pediatrics, All India Institute of Medical Science, New Delhi.