Serum Amyloid A Protein levels in Neonatal Sepsis

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Abstract

Introduction: Early diagnosis of Neonatal Sepsis continues to remain a significant global health challenge. The commonly studied biomarkers of sepsis include CRP, TNF-α, PCT, SAA and other acute-phase reactants, each having contradictory outcomes.

Aim & Objectives: To determine the levels of SAA protein in Neonatal Sepsis, to correlate SAA levels with CRP and blood culture and to evaluate the role of SAA as a marker of Neonatal Sepsis.

Materials and Methods: A hospital based prospective cohort study was carried out on 90 neonates ≥28 weeks gestational age with clinical signs and symptoms of sepsis. Serum sample was collected for estimation of SAA and CRP at the onset of clinical signs and symptoms of sepsis prior to start of antibiotic therapy.

Results: The study subjects were grouped based on the blood culture report into Culture-positive (n=40) and Culture-negative (n=50) groups. SAA showed sensitivity, specificity, PPV, NPV of 95%, 82%, 81%, and 95% respectively when compared to CRP which showed 92.5%, 10%, 45.12% & 62.5% respectively. Platelet count showed highest specificity of 92%.

Conclusion: The above findings support the use of SAA in the diagnosis of Neonatal Sepsis.

Keywords: SAA, Neonatal Sepsis, CRP, Haematological parameters in neonatal sepsis

Introduction

Neonatal sepsis refers to the systemic infection of neonates during 0–28 days after birth.(1) In spite of the advances in medicine, neonatal sepsis still remains a major diagnostic challenge. The early clinical signs and symptoms are subtle, vague, nonspecific, and there is no single ideal reliable marker available for the diagnosis. As a result, empirical antimicrobial therapy is often commenced on clinical suspicion of infection, thus increasing the risk of adverse effects of drugs and the development of drug resistance.(2,3)

Conventional biochemical and haematological tests used for the diagnosis of sepsis are C-reactive protein (CRP), Total Leukocyte Count (TLC), absolute neutrophil count (ANC), immature/total neutrophil ratio (I:T) and platelet count (PLT).(3,4) However, these tests are nonspecific and have low sensitivity and differing specificity.(3,4) Although positive blood culture is the gold standard for diagnosis of neonatal sepsis, it has certain drawbacks such as prolonged time period before reporting, low sensitivity and high incidence of false-negative results.(3,4)

During severe bacterial infection, increased levels of CRP are observed as part of an early innate immune response. Although an acute-phase reactant, some studies have shown that CRP cannot reliably differentiate between systemic inflammatory response and sepsis.(2,3)

Therefore, the accurate diagnosis of neonatal sepsis continues to pose a major diagnostic challenge, making it imperative to find dependable and reliable diagnostic bio-markers to enable efficient diagnosis and management of neonatal sepsis.

Serum amyloid A (SAA), a group of polymorphic apolipoproteins, that are mainly produced by the liver, have been proposed as a new diagnostic marker of bacterial infection.(4,5) But, some studies have found conflicting results.(2,6) The aim of this study, therefore, was to evaluate the role of SAA and CRP as early diagnostic markers neonatal sepsis in comparison to that of blood culture and haematological parameters like TLC and PLT count.

Materials and Methods

Study Design: This prospective cohort study was carried out at the neonatal intensive care unit (NICU) in our hospital from January 2014 to January 2015. The study was conducted on 90 neonates with gestational age ≥28 weeks with clinical signs and symptoms of neonatal sepsis. The study protocol was approved by the Ethical committee of the institution**.**

Method of Collection of Data:

Inclusion Criteria: The inclusion criteria were neonates who were admitted to the NICU with signs suggestive of sepsis like lethargy and poor cry, poor perfusion (capillary refill time >2 s), respiratory distress (respiratory rate > 60/min), hypoglycaemia (<40 mg/dL) or hyperglycaemia (>125 mg/dL), vomiting, diarrhoea, and abdominal distension.(1)

The maternal criteria included intrapartum fever, foul smelling, and/or meconium-stained liquor amnii, prolonged rupture of membrane (>24 h), and more than three vaginal examinations during labour. Sepsis screen was done in neonates with presence of more than or equal to two risk factors.(1)

Exclusion Criteria: The neonates with traumatic tissue injury, laboratory findings suggestive of inborn errors

of metabolism and congenital anomalies, history of perinatal and postnatal asphyxia, and neonates who were on anti-biotics or those who developed the signs of sepsis within 72 h of discontinuation of antibiotics were excluded from the study.[1]

Sample Collection: At the onset of clinical signs and symptoms of sepsis prior to the commencement of antibiotic therapy, serum sample was drawn for sepsis screen panel. After written informed consent was taken from either of the parents/guardians, blood sample sent to the Biochemistry Laboratory for CRP was aliquoted, labelled, and stored at −20°C for assay of SAA. CRP estimation was done on the samples on Roche Cobas 6000 c501 fully automated analyzer by immunoturbidimetric method.[7] The blood culture reports and haematological parameters of neonates chosen to be a part of the study were recorded. SAA assay was measured by Human SAA ELISA KIT quantitative sandwich enzyme immunoassay technique.[8]

Statistical Analysis of Data: All the quantitative parameters were described in terms of descriptive statistics, mean, and standard deviation. Qualitative parameters were expressed as proportions. The correlation of SAA and the CRP level with the haematological parameters (TLC, and PLT count) and the blood culture for diagnosis of neonatal sepsis was compared statistically using Student's *t*-test for independent samples. The level of significance was taken as p <0.05. The correlation between SAA and CRP was estimated through Pearson's correlation coefficient. Receiver operating characteristic (ROC) curve was plotted using MedCalc statistical software version, 15.10.0 for Windows (MedCalc Software bvba; Ostend, Belgium).

Result

The baseline characteristics of the neonates are shown in Table 1. Among the study subjects male babies formed 57.7% and female babies formed 42.3%. The mean age of neonates in the study was 4.06 ± 6.9 days (Fig. 1). The mean gestational age (weeks) was 34.45 ± 3.61. 63.3% of the subjects were preterm (<37 weeks gestational age) and 36.7% were term (gestational age ≥37 weeks) babies. The mean ± SD of birth weight (g) was 2,161 ± 920. Low birth weight (LBW) (<2,500g) was seen in 51 (56.7%) neonates, whereas 39 (43.3%) of the neonates were of normal birth weight.

Table 1: Baseline characteristics of the study subjects

Characteristics	n=90
Gender	
Male (n, %)	52 (57.7)
Female (n, %)	38 (42.3)
Mean ± SD of age (in days) at sampling	4.06 ± 6.9
Gestational Age (weeks) (Mean ± SD)	34.45 ± 3.61
No. of Preterm (<37 wks gestational age) (n, %)	57 (63.3)
No. of Full term (37-42 wks gestational age) (n, %)	33 (36.7)
Birth weight (gm) (Mean ± SD)	2161 ± 920
No. of normal birth weight (≥2500gm) (n, %)	39 (43.3)
No. of low birth weight (<2500gm) (n, %)	51 (56.7)

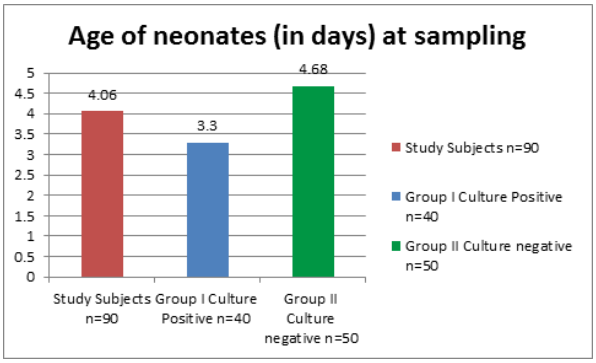

Fig. 1: Age of neonates at the time of sampling

Based on the blood culture report the study subjects were divided into two groups. Group I: culture positive, consisting of 40 neonates and group II: culture negative, consisting of 50 neonates. A comparison between the two groups (Table 2) showed the mean age in days in Culture positive group was 3.3 ± 6.7 while in Culture negative group was 4.68 ± 7.10 (Fig. 1). No significant difference was found between the groups regarding age, gender, and mode of delivery. Significant differences were found when birth weight, gestational age, duration of admission, and number of deaths in hospital were considered. In group I, 70% neonates were born preterm (gestational age <37 weeks), and, in group II, 58% of neonates were born preterm (p = 0.24).

Table 2: Showing comparison of demographic data in Group I and Group II

	Group I Culture Positive n=40 (%)	Group II Culture negative n=50 (%)	P value
Mean ± SD age in days	3.3 ± 6.7	4.68 ± 7.10	0.35
Gender			
No. of Male neonates (%)	20 (50)	32 (64)	0.181
No. of Female neonates (%)	20 (50)	18 (36)	
Mean ± SD Birth Weight (gm)	1800 ± 930	2450 ± 800	0.0005
No. of normal birth weight (≥2500gm) neonates (%)	12 (30)	27 (54)	0.022
No. of low birth weight (<2500gm) neonates (%)	28 (70)	23 (46)	
Mean ± SD Gestational age in weeks	33.3 ± 4.09	35.38 ± 2.9	0.005
No. of Preterm (<37 wks gestational age) neonates (%)	28 (70)	29 (58)	0.24
No. of Full term (37-42 wks gestational age) neonates (%)	12 (30)	21 (42)	
Mode of delivery			
No. of Normal Delivery (%)	15 (37.5)	18 (36)	0.88
No. of LSCS (%)	25 (62.5)	32 (64)	
Mean ± SD Duration of admission in days	28.675 ± 19.47	14.72 ± 13.09	0.001
No. of Deaths (%)	12 (30)	6 (12)	0.033

Table 3 show a comparison of the laboratory investigations between the groups I and II. There was a statistically significant difference between groups I and II in mean ± SD of Total Leukocyte Count and platelets. The mean ± SD of serum CRP (mg/dL) and SAA (µg/mL) values were significantly higher in culture-positive group (13.0±7.4, 47.4±23.4, respectively) when compared with the culture-negative group (4.6±3.13, 7.2±3.9, respectively) ($p < 0.05$). There was no statistically significant difference between the groups when Mean ± SD of haemoglobin was considered.

Table 3: Laboratory Investigations in study subjects

Quantitative Variables	Group I Culture positive (n=40)	Group II Culture negative (n=50)	p Value (student t test)
Mean ± SD Hemoglobin in g%	15.42 ± 3.91	15.5 ± 3.23	0.91
Mean ± SD Total Leukocyte Count TLC ($10^3/mm^3$)	16.17 ± 6.24	11.2 ± 4.61	<0.05
Mean ± SD Platelet count ($10^3/mm^3$)	159.93 ± 69.78	240 ± 65.99	<0.05
Mean ± SD CRP (mg/dL)	13.0 ± 7.4	4.6 ± 3.13	<0.05
Mean ± SD Serum Amyloid A[SAA] (µg/mL)	47.4 ± 23.4	7.2 ± 3.9	<0.05

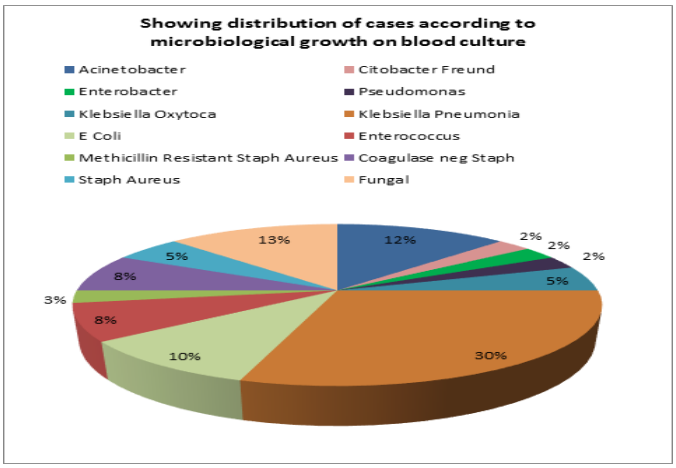

Fig. 2: Causative microorganisms in the culture positive group

Fig. 2 shows that the *Klebsiella* sp. in 35% was commonly isolated on blood culture, followed by *Staphylococcus aureus* in 16%, and *Acinetobacter* sp. in 12% of the culture-positive neonates.

On comparison of laboratory investigations according to the microorganism isolated on culture, a statistically significant difference was found only when mean ± SD of platelet count was considered. No statistically significant differences were found in the mean ± SD for SAA, CRP and Total Leukocyte Count where gram-positive, gram-negative, and fungal organisms were isolated. (Table 4 and Fig. 3)

A statistically significant strong positive correlation was observed between SAA and CRP values of all the study subjects (r = 0.775, p < 0.00001) [Fig. 4]. A weak positive correlation was found between Serum Amyloid A and Total Leukocyte Count (r= 0.3367, p < 0.05.) and Haemoglobin levels respectively (r= 0.0117 p = 0.912847) [Fig. 5 and 6]. A weak negative correlation between Serum Amyloid A and platelet count r= -0.4572 was observed (Fig. 7).

Table 4: A comparison of Laboratory investigations according to the microorganism isolated

	Gram Positive (n=9)	Gram Negative (n=26)	Fungal (n=5)	p value
SAA(µg/ml) Mean ± SD	61.22 ± 38.20	43.04 ± 16.61	45.44 ± 11.60	0.130
CRP (mg/dl) Mean ± SD	15.40 ± 12.93	12.20 ± 5.13	13.02 ± 13.56	0.633
Platelet Count (10^3/mm^3) Mean ± SD	82 ± 44.37	176.28 ± 58.40	189.2 ± 62.82	< 0.001
Total leukocyte count (10^3/mm^3) Mean ± SD	15.23 ± 3.13	16.63 ± 6.20	15.08 ± 9.3	0.774

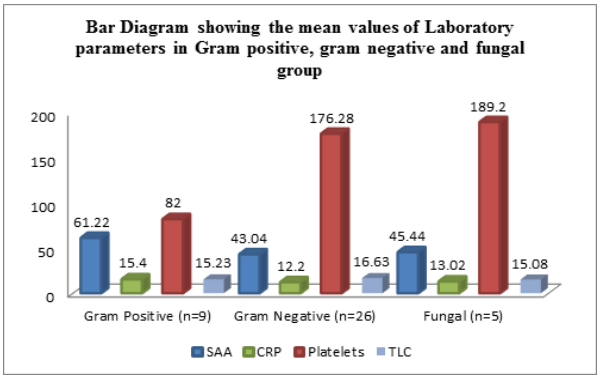

Fig. 3: Laboratory parameters according to the organism isolated

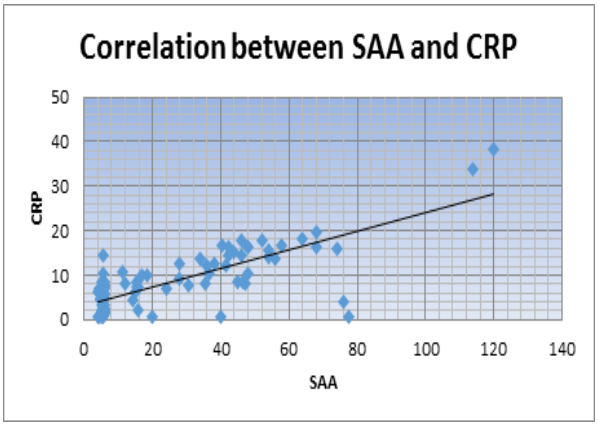

Fig. 4: Correlation between SAA and CRP

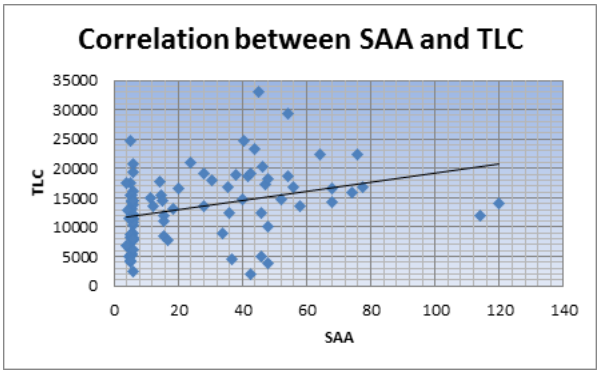

Fig. 5: Correlation between Serum Amyloid A and Total Leukocyte Count

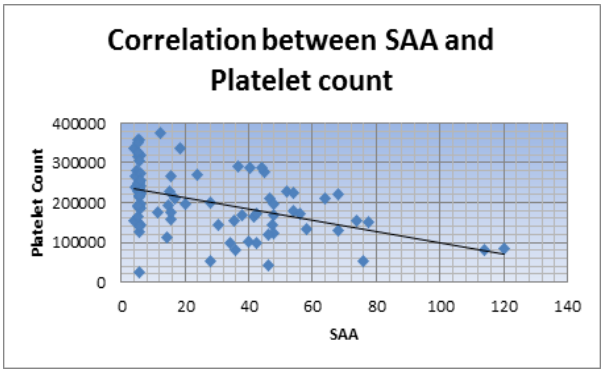

Fig. 7: Correlation between Serum Amyloid A and Platelet Count

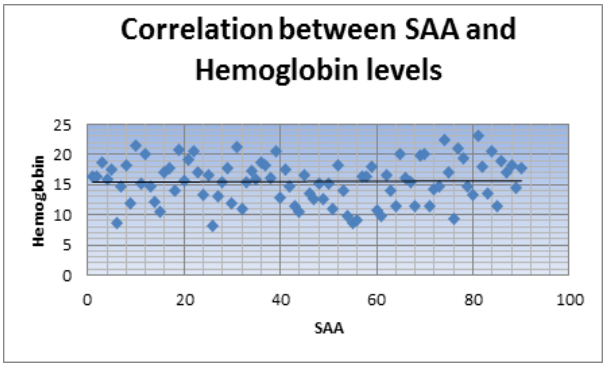

Fig. 6: Correlation between Serum Amyloid A and Hemoglobin

On comparing the laboratory investigations (Table 6), total leukocyte count was abnormal in 67.5% of the 40 blood positive cultures and 28% of the 50 blood negative cultures. Platelet count was low (< 150 $x10^3/mm^3$) in 42.5% and 8% of neonates in the culture-positive and culture-negative groups respectively. Among the culture-positive group, 92.5% of neonates showed serum CRP levels ≥ 1 mg/L, whereas 90% of culture-negative neonates showed serum CRP levels ≥1 mg/dL. In culture-positive group, 95% of neonates and only 18% of the culture-negative neonates showed SAA levels ≥ 10 µg/mL.

Table 6: Comparison of laboratory investigations among culture positive and negative groups

Parameters	Cut-offs	Study subjects n=90 n (%)	Culture positive n=40 n (%)	Culture negative n=50 n (%)
Total Leukocyte Count in $10^3/mm^3$	Above 15 or below 5	41(45.5)	27 (67.5)	14 (28)
	Normal 5-15	49 (54.4)	13 (32.5)	36 (72)
Platelets in $10^3/mm^3$	Below 150	21(23.3)	17 (42.5)	4 (8)
	Normal 150-400	69 (76.6)	23 (57.5)	46 (92)
CRP in mg/dL	Above ≥ 1	82 (91.1)	37 (92.5)	45 (90)
	Normal < 1	8 (8.9)	3 (7.5)	5 (10)
SAA in µg/mL	Above ≥ 10	47 (52.2)	38 (95)	9 (18)
	Normal < 10	43 (47.8)	2 (5)	41 (82)

In the Culture-negative group, normal levels of Total Leukocyte Count, Platelets, CRP and Serum Amyloid A were seen in 72%, 92%, 10% and 82% of the neonates respectively.

A statistically significant association was seen between the SAA results and the blood culture results ($p < 0.001$) (Table 7). There was no statistically significant association seen between the CRP results and the blood culture results ($p > 0.05$) (Table 8).

Table 7: Comparison of Serum Amyloid A values in Culture positive and culture negative groups

SAA in µg/mL	C Negative		C Positive		χ^2	P-Value
	N	%	n	%		
≥ 10	9	18%	38	95%	38.455	<0.001*
< 10	41	82%	2	5%		
Total	50	100%	40	100%		

Table 8: Comparison of CRP values in Culture positive and culture negative groups

CRP in mg/dL	C Negative		C Positive		χ^2	P-Value
	n	%	n	%		
≥ 1	45	90%	37	93%	2.679	0.102

The study subjects were 90, but there were three neonates (one in culture-positive group and two in the culture-negative group), who took a voluntary discharge against medical advice. Among the 87 neonates that were followed up till discharge, 18 neonates (12 in culture-positive group and six in the culture-negative group), died. Among the non-survivors, CRP was elevated ≥ 1 mg/dL in 94.4% of the non-survivors, and SAA was above ≥ 10 µg/mL in 72.2% of the non-survivors [Table 9]. Among the survivors, 53.62% showed normal SAA levels. Abnormal Total leukocyte Count and platelet counts were found in 66.6% and 16.6% of the non-survivors respectively. Amongst the survivors, 75.3% had normal platelet counts and 53.62% of survivors had normal SAA levels.

Table 9: Comparison of laboratory investigations in Survivors and Non-Survivors

Parameters	Cut-offs	Survivors n=69 n (%)	Non-Survivors n=18 n (%)
Total Leukocyte Count in $10^3/mm^3$	Above 15 or below 5	28 (40.6)	12(66.6)
	Normal 5-15	41(59.4)	6(33.3)
Platelets in $10^3/mm^3$	Below 150	17 (24.63)	3(16.6)
	Normal 150-400	52(75.3)	15(83.3)
CRP in mg/dL	Above ≥ 1	62(89.8)	17(94.4)
	Normal < 1	7(10.1)	1(5.55)
SAA in µg/mL	Above ≥ 10	32(46.37)	13(72.2)
	Normal < 10	37(53.62)	5(27.7)

Sensitivity was maximum for Serum Amyloid A at a cut off of 10 µg/mL(95%) and least for Total Leukocyte Count Above 15 or below 5 X $10^3/mm^3$ (42.5%). Specificity was highest for Platelets Count below 150 X$10^3/mm^3$ (92%) whilst for Serum Amyloid A it was 82%. Serum Amyloid A had the maximum Positive Predictive value (81%) and negative predictive value (95%) amongst other laboratory investigations for neonatal sepsis (Table 10).

Table 10: Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value of laboratory investigations in Neonatal Sepsis

Tests with cut –off values	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
CRP ≥ 1 mg/dL	92.5%	10%	45.1%	62.5%
SAA ≥ 10 µg/mL	95%	82%	81%	95.3%
Total Leukocyte Count above 15 or below 5 X $10^3/mm^3$	67.5%	72%	65.8%	73.4%
Platelets below 150 X$10^3/mm^3$	42.5%	92%	81%	66.6%

In order to study the diagnostic accuracy of the laboratory tests for the diagnosis of neonatal sepsis, ROC curves were plotted [Fig. 8]. The area under the ROC curve (AUC) was 0.9683 for SAA compared with serum CRP AUC that was 0.868, with a difference of 0.37 in AUC and the difference being statistically significant (p = 0.039). From the ROC curves SAA, Serum CRP, Total Leukocyte Count and Platelet Count had optimal cut-offs of ≥ 12 µg/mL, ≥ 7.5 mg/dL, >12, 500 X $10^3/mm^3$ and ≤180000 X $10^3/mm^3$ respectively in this study.

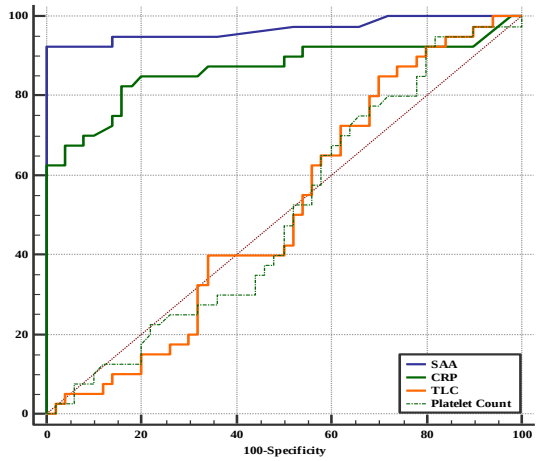

Fig. 8: ROC curve comparing the laboratory investigations in Neonatal sepsis

Discussion

Despite advanced and improved management strategies, neonatal sepsis remains a major cause of neonatal morbidity and mortality.[9]

Although, the most reliable test for diagnosing sepsis is a blood culture, but that too could give erroneous results owing to contamination or inadequate sampling, and reports are available only 72 h later.[3,4] Conventional laboratory tests in the screening and diagnosis of neonatal sepsis include total leukocyte count (TLC), band to total polymorphonuclear cells ratio, absolute neutrophil count, micro-erythrocyte sedimentation rate, platelet counts, and CRP levels—each one of them having varied performance characteristics and differing in terms of sensitivity and specificity.[3,4]

Male neonates (57.7%) formed a majority of the study subjects in our study [Table 1] which was similar with the results of study done by Mohsen et al.[4] and Sriram.[10] The male preponderance may be linked to the X-linked immunoregulatory gene factor which contributes to the host's susceptibility to infections.[11]

Sixty-three percent of the study subjects were preterm (<37 weeks gestational age) and 36% were term (gestational age ≥37 weeks) [Table 1]. The study done by Labib et al.,[12] showed that majority of sepsis occurred in LBW and premature infants (68.6% each). Impaired humoral and cellular defence mechanisms and invasive life support systems make the premature neonate susceptible to overwhelming infection.[13]

In our study, statistically significant difference was seen in the birth weight (g) between culture-positive group (1,800 ± 930) and in culture-negative group (2,450 ± 800). The study done by Prashant et al showed significant difference in the birth weight between culture-positive (2,388 ± 670) and culture-negative group (2,728 ± 673).[14] This was inconsistent with the results obtained in few other studies.[4,12]

The present study showed that there was a statistically significant difference between groups I and II in mean ± SD of Total Leukocyte Count, platelets, Serum CRP and Serum Amyloid A. A significant low mean platelet count (132.6 ± 30.6 x 10^3/mm^3) was seen in cases in the study done by Mohsen et al when compared to controls (148.5 ± 27.610^3/mm^3) ($p<0.05$)[4]. This was in contradictory with the study done by Thurlbeck and Meintoch,[169] which stated that, TLC is the least useful index for sepsis because the normal range is so wide, varies with gestational and postnatal age. Labib et al., reported that the mean CRP level was significantly higher in patients (32.91 ± 25.42) than in control subjects (7.50 ± 2.12).[12] In agreement to our results, Mohsen et al.[4] found a statistically significant difference in SAA levels between the study and control groups [40.16 ± 35.17 (µg/mL) and 6.45 ± 2.42 (µg/mL), respectively.

By comparing the laboratory investigations according to the microorganism isolated on culture and application of analysis of variance (ANOVA) test, the mean ± SD of serum CRP and SAA were highest in gram-positive infections and platelet count was lowest in infections with gram positive bacteria. Total leukocyte count was maximum in gram negative infections. This was contradictory to the study done by Mohsen et al.,[4] who found that the gram-negative sepsis produced a more pronounced elevation of SAA levels than what occurred with gram-positive sepsis.

There was a statistically significant strong positive correlation between SAA and CRP values of all the study subjects ($r = 0.775$, $p < 0.00001$) [Fig. 4]. A weak positive correlation was found between Serum Amyloid A and Total Leukocyte Count (r= 0.3367, p < 0.05.) and Hemoglobin levels respectively (r= 0.0117 p = 0.912847) (Fig. 5, 6). A weak negative correlation between Serum Amyloid A and platelet count r= -0.4572, Fig. 7). Mohsen et al showed similar significant positive correlation between SAA and CRP levels (r= 0.483, p= <0.01) whereas, a non-significant positive correlation was observed between the SAA protein level and the TLC in the studied cases (r = 0.203, P = > 0.05)[4]. In contradiction to our results the study conducted by Ucar et al showed that the serum levels of CRP negatively correlated with the levels of SAA[6]. A higher proportion of the neonates with sepsis had raised Serum Amyloid A levels (95% vs. 18 %) than those without sepsis similar to as seen in the study done by Mohsen et al[4]. Raised CRP levels were seen in those with sepsis (92.5%) as well as those without sepsis (90%).

On comparison of laboratory investigations, sensitivity was maximum for Serum Amyloid A at a cut off of 10 µg/mL (95%) and least for Platelet Count below 150 X10^3/mm^3 (42.5%) (Table 10). Sensitivity of CRP at a cut-off of ≥ 1 mg/dL was 92.5%. This implies that the ability of Serum Amyloid A to correctly provide a diagnosis of neonatal sepsis in a neonate with

signs and symptoms of sepsis is better than Serum CRP. In the presence of sepsis, the probability of Serum Amyloid A being raised above the cut-off is high. It is also very unlikely that neonates with serum Amyloid A levels <10 µg/mL, but with signs and symptoms of sepsis will have blood culture positive neonatal sepsis. In the study done by Franz AR et al, he found that the sensitivity of CRP at presentation was only 40% and 60% of subsequently proven sepsis episodes had a normal initial CRP indicating that there is generally a delay of up to 24 hours between onset of symptoms of infection and a rise in serum CRP.

Specificity was 10% for CRP and 82% for SAA but was highest for low Platelet Count (92%) [Table 8]. This signifies that there is a high probability of neonates with normal SAA levels when there is no neonatal sepsis. It is also very likely that the neonate with signs and symptoms of sepsis will have blood culture-positive neonatal sepsis if SAA levels are ≥ 10 µg/mL. In the study done by Ahmad et al,[16] he concluded that severe thrombocytopenia is one of the most common haematological parameter during early sepsis and can act as an early diagnostic marker of neonatal sepsis. In this study, PPV [Table 10] for SAA was 81%, whereas, for Serum CRP, it was 45.1%, which indicates that, among the neonates who showed SAA levels ≥10 µg/mL, the probability of sepsis was 81%. The PPV of SAA in this study was higher than that of CRP and TLC. NPV [Table 10] for SAA was 95.3%, whereas, for serum CRP, it was 62.5%. This signifies that, among the neonates who showed SAA levels <10 µg/mL, the probability of being disease-free was 95.3%. These results came in agreement with Arnon et al.,[17] who showed a high PPV of SAA compared with that of CRP (86%).

In order to study the diagnostic accuracy of the laboratory tests for the diagnosis of neonatal sepsis, ROC curves were plotted [Fig. 8], which showed that AUC for SAA (0.986) was significantly higher than serum CRP (0.868). From the ROC curves, Serum Amyloid A, Serum CRP, Total Leukocyte Count and Platelet Count had optical cut-offs of ≥ 12 µg/mL, ≥ 7.5 mg/dL, >12, 500 X 10^3/mm^3 and ≤180000 X 10^3/mm^3 respectively in the present study.

The limitations of this study are a small sample size, not including healthy neonates as control subjects and lack of serial sample measurement.

Conclusion

The ability to exclude sepsis in neonates in the NICU is clinically very important. The high negative predictive value for SAA achieved in this study would be very helpful to the clinician in making the decision as to whether it is safe to withhold or discontinue antibiotic therapy. Therefore, SAA may be included as a promising, diagnostic and prognostic marker of neonatal sepsis. Further studies with larger sample size and longitudinal nature must be undertaken.

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