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Evaluation of laboratory markers in early diagnosis of neonatal sepsis

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Abstract: Background and Aim: Sepsis is a commonest cause of morbidity and mortality in the newborns and probably accounts for 30 to 50 percentage of neonatal death worldwide in developing countries so the study aimed to find out the most reliable laboratory parameter in early diagnosis of neonatal sepsis in comparison with blood culture in terms of Sensitivity, Specificity, Positive predictive value, Negative predictive value.
Material and Methods: A cross sectional study was conducted in the NICU and SCNU at Institute of Child Health, Government Medical College, Kottayam to evaluate the laboratory markers like total WBC count, I-T ratio, CRP, platelet count in early diagnosis of neonatal sepsis in comparison with blood culture. After taking informed consent from parents and permission from ethical committee, neonates brought to neonatology unit were selected by purposive sampling technique. Sample size was 120. All neonates having suspected sepsis were included. All neonates included in the study were started on empirical antibiotics after drawing samples for blood cultures, total WBC count, I-T.
Results: This study was designed to find out the most reliable parameter in early diagnosis of neonatal sepsis like total count, CRP, I-T ratio and platelet count in comparison with blood culture in terms of sensitivity, specificity, PPV and NPV.A total of 120 babies were studied who satisfied the inclusion criteria and ruling out those meeting exclusion criteria. Out of 120 babies studied early onset sepsis include 52.5% and late onset of sepsis include 47.5%.
Conclusion: This study proves that CRP is a test with good sensitivity and I-T ratio with maximum specificity but least sensitivity. These can be used for diagnosis of neonatal sepsis and treatment can be initiated before the blood culture results come.

Keywords: Sensitivity; Specificity; Positive predictive value; Negative predictive value; CRP; Sepsis.

1. Introduction

Sepsis is a commonest cause of morbidity and mortality in the newborns and probably accounts for 30 to 50 percentage of neonatal death worldwide in developing countries [1]. Sepsis is well-defined as a "clinical syndrome characterized by systemic signs/symptoms and bacteraemia during the 1st month of life". Sepsis is known as 'early onset' disease if present during1st3 days of life and considered as 'late onset' if it follows after 3 days. Of newborns with early-onset sepsis, 85% present within 24 hours, 5% present at 24-48 hours, and a smaller percentage present within 48-72 hours. Onset is most rapid in premature neonates [2].

Neonatal sepsis can be classified into two major categories depending up on the onset. Early onset sepsis (EOS): It presents within the first 72 hours of life [3]. In severe cases, the neonate may be symptomatic at birth. Infants with EOS usually present with respiratory distress and pneumonia. The source of infection is generally the maternal genital tract. Some maternal/ perinatal conditions have been associated with an increased risk of EOS. Late-onset sepsis (LOS) occurs after 72 hours of life and is acquired from the caregiving environment. Trends in late-onset sepsis show an increase in coagulase-negative staphylococcal sepsis; most of these isolates are susceptible to first-generation cephalosporins [4].

The infant's skin, respiratory tract, conjunctivae, gastrointestinal (GI) tract, and umbilicus may become colonized from the environment, and such colonization to the possibility of late-onset sepsis from invasive microorganisms. Vectors for such colonization may include vascular or urinary catheters, other indwelling lines, or contact with caregivers who have bacterial colonization [5].

2. Material and Methods

It was a cross-sectional study conducted at Inborn and outborn neonatal unit in Govt. medical College Kottayam for a period of 12 months after ethical clearance from IRB.

As per study by DR Zeeba ur Zaka Rab, DR. Monika Ka and Veena Gupta115 on laboratory markers in sepsis screen in early diagnosis of neonatal sepsis in neonatalogy unit Jawaharlal institute of medical sciences, Uttar Pradesh, prevalence was 3 percentage. Sensitivity of platelet count in neonatal sepsis was least among the sepsis screen parameters.

$$
\begin{aligned}
N_{(Sp)} &= Z^2_{a/2} \times \frac{\text{Sensitivity} \times (1 - \text{Sensitivity})}{d^2} \times \frac{p}{1-p}, \\
N_{(Sn)} &= Z^2_{a/2} \times \frac{\text{Specificity} \times (1 - \text{Specificity})}{d^2} \times \frac{1-p}{p}, \\
Z_{a/2} &= 1.96, \\
\text{Prevalence} &= 3\%, \\
N_{(Sp)} &= \frac{3.84 \times 37.5 \times 62.5}{25 \times 3} = 120.
\end{aligned}
$$

Consecutive cases, satisfying the inclusion criteria and sample size, admitted in inborn nursery, outborn nursery, and followed up in high risk newborn clinic in Department of Paediatrics, Govt. Medical College Kottayam during the study period.

2.1. Inclusion criteria

- All babies from 0 to 28 days of life with clinical suspicion of sepsis.
- Gestational age more than 28 weeks.

2.2. Exclusion criteria

- Birth asphyxia.
- Neonates already received antibiotics.
- Neonates suspected to have inborn error of metabolism.

3. Statistical Analysis

The statistical analysis was performed using SPSS for windows version 22.0 software (Mac, and Linux). The findings were present in number and percentage analyzed by frequency, percent, and Chi-squared test. Chi-squared test was used to find the association among variables. The critical value of P indicating the probability of significant difference was taken as <0.05 for comparison.

4. Results

Among the 120 babies 62 (51.7%) females and 58(48.3%) males were included in study. Among the 120 babies studied 60 babies are preterm and 60 babies are term. Out of 120 babies studied 39(32.5%) babies were SGA, 78(65%) babies were AGA, and 3(2.5%) babies were LGA As per Table 1 according to chi-square test, p value 0.789, found to be statistically insignificant neonatal sex and blood culture had no correlation

As per Table 2 According to chi-square test, p value 0.702, found to be statistically insignificant gestational age and blood culture had no correlation.

As per Table 3 According to chi-square test, p value 0.51, found to be statistically insignificant so WBC count and postnatal age had no correlation.

Table 1. Comparison of neonatal gender and blood culture

Sex	Blood culture				Total		χ^2	Df	P
	Positive		Negative						
	N	%	N	%	N	%			
Female	21	33.9	41	66.1	62	100	0.072	1	0.789
Male	21	36.2	37	63.8	58	100			
Total	42	35	78	65	120	100			

Table 2. Comparison of gestational age and blood culture

Gestational age	Blood culture				Total		χ^2	Df	P
	Positive		Negative						
	N	%	N	%	N	%			
Term	22	36.7	38	63.3	60	100	0.147	1	0.702
Preterm	20	33.3	40	66.7	60	100			
Total	42	35	78	65	120	100			

Table 3. Comparison of postnatal age with WBC count.

Total WBC count	Age at onset of symptoms				Total		χ^2	df	P
	<3 days		>3 days						
	N	%	N	%	N	%			
<4000 / >20000	25	49	26	51	51	100	0.431	1	0.512
4000-20000	38	55.1	31	44.9	69	100			
Total	63	52.5	57	47.5	120	100			

Table 4. Comparison of neonatal gender and CRP

CRP	Gender				Total		χ^2	df	P
	Female		Male						
	N	%	N	%	N	%			
>15 mg/dl	46	51.1	44	48.9	90	100	0.044	1	0.833
<15 mg/dl	16	53.3	14	46.7	30	100			
Total	62	51.7	58	48.3	120	100			

Table 5. Comparison of gestational age and IT ratio

I-T Ratio	Gestational age				Total		χ^2	df	P
	Term		Preterm						
	N	%	N	%	N	%			
>0.2	5	55.6	4	44.4	9	100	0.12	1	0.729
<0.2	55	49.5	56	50.5	111	100			
Total	60	50	60	50	120	100			

Table 6. Comparison of total WBC count and mode of delivery

Total WBC count	Mode of delivery				Total		χ^2	df	P
	LSCS		Vaginal						
	N	%	N	%	N	%			
<4000 / >20000	21	41.2	30	58.8	51	100	1.422	1	0.233
4000-20000	36	52.2	33	47.8	69	100			
Total	57	47.5	63	52.5	120	100			

According to chi square test, p value obtained was 0.833, which statistically insignificant so neonatal gender and CRP not comparable. According to chi square test, p value obtained was 0.729, which statistically insignificant so gestational age and I T ratio not comparable. According to chi square test, p value obtained was 0.233, which statistically insignificant so mode of delivery and WBC count not comparable. According to chi square test, p value obtained was 0.945, which statistically insignificant so mode of delivery and platelet count not comparable. According to chi square test, p value obtained was 0.158, which is statistically insignificant so birth weight and WBC count had no correlation. As per Tables 9 and 10, among the markers studied CRP has highest sensitivity was CRP 90.5%, the most specific parameter was I -T ratio with a sensitivity of 94.9%. sensitivity of platelet count, WBC count, I-T ratio were 19%, 11.9%, 40.5% respectively, specificity of CRP, WBC count, platelet count were 33.3%, 56.4%, 91% respectively, positive predictive values of I-T ratio, platelet count, CRP, WBC count .

5. Discussion

The study was conducted with an aim to find out the most reliable parameter in early diagnosis of neonatal sepsis like total count, CRP, IT ratio, platelet count in terms of sensitivity, specificity, positive predictive value, negative predictive value in comparison with blood culture which is considered as the gold standard. These markers are simple test. Moreover, it gives quick results. Hence it can be used for diagnosis and treatment of neonatal sepsis if found to have an acceptable validity. It was a cross sectional study. The minimum sample size was calculated to be 120. A total of 120 babies were studied who satisfied inclusion criteria and ruling out those satisfying the exclusion criteria. All these babies, after taking consent had their blood sampled for Total WBC count, I T ratio, platelet count, CRP and blood culture. Other investigations including Urine studies and CSF studies were done if indicated.

A similar study was done by authors CRP was having maximum sensitivity of 87.8% followed by total leucocyte count. I-T ratio had maximum sensitivity of 85.1% [6–8]. It can be used as an important parameter in infant at risk of septicaemia with high sensitivity and I-T ratio with maximum specificity. CRP also has got prognostic value [9–11] CRP had better diagnostic utility with a specificity of 82.14% and specificity of 80.1%, I-T ratio had highest specificity of 100% and sensitivity of 78.5%sensitivity (73.1%), positive predictive value

Table 7. Comparison of modes of delivery with platelet count

Platelet count	Mode of delivery				Total		χ^2	df	P
	LSCS		Vaginal						
	N	%	N	%	N	%			
<1 Lakh	7	46.7	8	53.3	15	100	0.005	1	0.945
>1 lakh	50	47.6	55	52.4	105	100			
Total	57	47.5	63	52.5	120	100			

Table 8. Comparison of total WBC count with birth weight

Total WBC count	**Birth weight**						**Total**		χ^2	**df**	**P**
	SGA		**AGA**		**LGA**						
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**			
<4000 / >20000	12	23.5	37	72.5	2	3.9	51	100	3.691	2	0.158
4000-20000	27	39.1	41	59.4	1	1.4	69	100			
Total	39	32.5	78	65	3	2.5	120	100			

Table 9. Comparison of I -T ratio with blood culture with Diagnostic values

		Blood culture		**Total**
		Positive	**Negative**	
IT Ratio	>0.2	5	4	9
	<0.2	37	74	111
	Total	42	78	120

Sensitivity	11.9
Specificity	94.9
PPV	55.6
NPV	66.7
Accuracy	65.8
LR+	2.3
LR-	0.93

Table 10. Diagnostic values of CRP

Sensitivity	90.5
Specificity	33.3
PPV	42.2
NPV	86.7
Accuracy	53.3
LR+	1.4
LR-	0.29

(61.3%) and negative predictive value (90%) than other used routine markers and all the routine markers are found to be highly specific in diagnosis of neonatal sepsis [12,13]. The specificity of TLC and ANC are 87.8% and 79.7% respectively [14,15].

My study has shown a high sensitivity for CRP of 90.5%. This indicates that the test is a good screening test, meaning CRP negativity can effectively rule out neonatal sepsis. CRP also showed high NPV, so good tool in ruling out neonatal sepsis. The study also showed a high specificity for I-T ratio 94.9% and a PPV of 55.6% which indicates that it is a test comparable to blood culture in diagnosing neonatal sepsis. The study also showed that platelet count also showed good specificity 91 percentage with PPV of 53.5% [16,17,19]. The above statements, means that, tests like CRP and I-T ratio can be used for early diagnosis of neonatal sepsis [**?**]. Empirical antibiotics can be started based on these tests results as blood culture results are time consuming and often negative.

6. Conclusion

This study proves that CRP is a test with good sensitivity and I-T ratio with maximum specificity but least sensitivity. These can be used for diagnosis of neonatal sepsis and treatment can be initiated before the blood culture results come. This indicates that CRP is a good screening test, meaning CRP negativity can effectively rule out neonatal sepsis. CRP also showed high NPV, so good tool in ruling out neonatal sepsis. Although I-T ratio had good specificity, the sensitivity was low. So, combination of these markers is better early diagnosis of neonatal sepsis. Neonatal factors like sex, gestational age, age of onset of symptoms, mode of delivery and birth weight were compared laboratory markers and found they do not have statistically significant except for postnatal age and platelet count.

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Conflicts of Interest: The authors declare that they do not have any conflict of interests.

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