To study the efficacy of screening panel including interleukin-6 in diagnosis of neonatal sepsis

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Abstract

Objective: To Study the Efficacy of Screening Panel, Including Interleukin 6, in Diagnosis of Neonatal Sepsis.

Materials and Methods: This prospective study was done from 2015-2016 in the Post Graduate department of Pediatrics of Subharti Medical College, Meerut. 100 neonates below the age of 28 days with a clinical suspicion of neonatal sepsis were enrolled in the study. Septic panel (WBC, ANC, I/T ratio, Micro ESR, CRP), IL-6 and blood culture were sent for screening. Data was collected and analyzed in babies having a positive blood culture. Septic panel in blood culture positive babies with \ge 3 variables of septic panel without IL-6, were compared with septic panel in blood culture positive babies with \ge 3 variables of septic panel with IL-6. Data was analyzed.

Result: Presence of the new marker (IL-6) with the septic panel shows a sensitivity of 65.71%, specificity of 96.92% and PPV of 92.0% against the septic panel without IL-6, which shows a sensitivity of 34.28%, specificity of 93.84% and PPV of 75.0%.

Conclusion: Septic panel with IL-6 has more sensitivity, specificity and positive predictive value as compared to septic panel without IL-6.

Keywords: Neonatal sepsis, Interleukin-6.

Introduction

Neonatal sepsis is defined as an invasive bacterial infection which occurs in the first 4 weeks of life. It is the commonest cause of neonatal mortality and is responsible for 30-50% of all neonatal deaths each year in developing countries.¹⁻³

It is estimated that up to 20% of neonates develop sepsis and approximately 1% die of sepsis related causes.² The World Health Organization (WHO) estimates that each year 4 million newborns, worldwide, die during the neonatal period.² Seventy-five percent of these deaths occur during the first week of life. About 25% to 45% neonatal deaths occur on the first day of life.³⁻⁵ In India the incidence of neonatal sepsis varies from 11 - 24.5/1000 live births.

The presenting features of sepsis in neonates are nonspecific and subtle, leading to a delay in diagnosis and treatment, there by worsening morbidity and mortality. Traditional septic screen does not have high specificity or sensitivity to detect sepsis in neonates; thus a new early septic marker (IL-6) was included in the septic screen panel anticipating that the sensitivity and specificity of the septic panel would increase.

Objective

To study the efficacy of screening panel including interleukin 6 in diagnosis of neonatal sepsis.

Materials and Methods Material

This prospective study was conducted in a tertiary care centre, Subharti Medical College, Meerut, over a periodofone year 2015-2016. A hundred neonates above 34 weeks gestation and below the age of 28 days admitted in the NICU or Nursery with clinical suspicion of neonatal septicaemia were included in the study.

Method

Blood was collected with all aseptic precautions and sent for estimation of total leukocyte count, absolute neutrophil count, I/T ratio, another sample was centrifuged and serum collected and preserved in a sterile container and refrigerated at -20°c for *IL 6 estimation*, a third sample was sent for blood culture.

IL-6 was be detected using a commercial ELISA kit provided by Diaclone and the cut off values were taken as 24.5pg/ml⁷

Absolute Neutrophil count was calculated and Micro ESR was noted.

The reports were collected and tabulated.

Observations and Results

The following statistics can be defined:

- 1. Sensitivity: probability that a test result will be positive when the disease is present (true positive rate, expressed as a percentage). = a / (a+b)
- 2. Specificity: probability that a test result will be negative when the disease is not present (true negative rate, expressed as a percentage). = d / (c+d)
- 3. Positive predictive value: probability that the disease is present when the test is positive (expressed as a percentage). = a/(a+c)
- 4. Negative predictive value: probability that the disease is not present when the test is negative (expressed as a percentage). = d/(b+d)

Table 1: Diagnostic statistics

Test	Disease Present	N	Disease Absent	n	Total
Positive	True Positive	а	False Positive	С	a+c
Negative	False Negative	b	True Negative	d	b+d
Total		a+b		c+d	

Significant Figures

Suggestive Significance (P value: 0.05<P<0.10) Moderately Significant (P value: 0.01<P ≤0.05)

Strongly Significant (P value: P≤0.01)

100 newborns with probable sepsis were studied.

Table 2: Particulars of the 100 neonates studied who had clinical suspicion of septicemia

Neonates characteristics	N=100 No of neonates		
Age in days			
0-3 days	84		
4-28 days	16		
Gender			
Male	57		
Female	43		
Gestational age			
Preterm	70		
Term	30		
Birth weight (gms)			
<1500	10		
1500-2500	60		
>2500	30		
Place of birth			
Intramural	36		
Extramural	64		

Table 3: Blood investigations of neonates with clinical sepsis

Blood Investigations	N=100 No of neonates				
WBC count					
<5000/cumm	20				
≥5000/cumm	80				
ANC					
<1750 /cumm	19				
≥1750/cumm	81				
Micro ESR at end of 1st hr					
Positive>10mm	25				
Negative< 10 mm	75				
I/T ratio					
<u>≥</u> 0.2	23				
<0.2	77				
CRP					
Positive >5 mg/dl	29				
Negative<5mg/dl	71				
IL 6					
Positive <u>></u> 24.65pg/ml	32				
Negative<24.65pg/ml	68				

	True positive	False	False	True
		Positive	Negative	Negative
WBC <5000	14	6	21	59
ANC <1750	15	4	20	61
Micro ESR	15	10	20	55
I/T ratio	10	13	25	52
CRP	22	7	13	58
IL -6	19	13	16	52
Combinations				
CRP+ WBC	7	11	28	54
CRP+ANC	9	10	26	55
CRP+MICRO ESR	10	15	25	50
CRP+ IL- 6	12	16	22	49
Any Variable >3 without IL-6	12	4	23	61
Any Variable >3 with IL-6	23	2	12	63

Table 4: Correlation of laboratory parameters in relation to blood culture (Growth/ No growth)

Table 5: Correlation of WBC Count, ANC, Micro ESR, I/T ratio, CRP, IL-6 and combinations with blood culture (Growth/No growth)

Septic screen parameters	Sensitivity	Specificity	PPV	NPV	Accuracy
WBC	40	90.76	70	73	14.59
ANC	42.85	93.84	78.94	75.30	15.61
Micro ESR	42.85	84.61	60	64.70	15.55
I /T ratio	28.5	80	43.4	67.75	10.52
CRP	62.85	89.23	75.86	81.69	22.58
IL-6	54.28	80	59.37	76.47	19.52
Combinations					
CRP+ WBC	20	83.07	38.88	65.8	7.54
CRP+ANC	28.71	84.61	47.36	67.90	9.55
CRP+MICRO ESR	28.57	76.92	40	66.66	10.5
CRP+ IL-6	37.14	75.38	44.82	69.01	13.49
Any Variable ≥3 Without IL-6	34.28	93.84	75.0	72.61	12.61
Any Variable ≥3 With IL-6	65.71	96.92	92.00	84.00	23.63

Discussion

Indirect markers of infection when collectively studied provide an extremely reliable index of early suspicion of neonatal sepsis and serve as a useful guide for initiating antibiotic therapy. Bacterial culture positivity gave definitive diagnosis of septicemia.

In this study out of 100 cases of suspected sepsis 35 cases were proven culture positive. It was observed that CRP had highest sensitivity, specificity, PPV and NPV followed by IL-6, micro ESR, absolute neutrophil count (ANC), WBC count and I/T ratio. Combination of septic panel without IL-6 test had a sensitivity of 34.28%, specificity of 93.84%, and positive predictive value of 75%. Septic panel with IL-6 had a sensitivity of 65.71%, specificity of 96.92%, and positive predictive value of 92.0%.

We have made two investigating septic panels (including WBC, ANC, Micro ESR and I/T ratio) which were considered.

- 1. Septic panel without IL-6
- 2. Septic panel with IL-6

In the first investigating Septic panel i.e. without IL-6, we observed that the sensitivity was 37.14%, specificity 75%, PPV 44.8% with significant p value. Taker R⁷ and Ramesh Bhat⁸ observed similar results in their studies too. Alistair et al⁹ and Gerdes et al¹⁰ observed high sensitivity and specificity in their studies.

In the second investigating Septic panel i.e. with IL-6, sensitivity was seen to be 65.71%, specificity 96.92% and PPV 92. All the parameters were increased with addition of IL-6 in the septic panel. In another study by Henrit et al (2001) similar results were obtained as in this study, with a significant p value.

On comparing the two groups we found that all parameters were statistically significant in the group with IL-6.

Summary and Conclusion

To detect early sepsis in neonates a new early septic marker (IL-6) was included in the septic screen in this study, which detects sepsis even before the appearance of clinical features. Using this early marker it was observed that independently IL-6 was not a good marker but if included in

the septic panel then the efficacy of the septic panel in terms of sensitivity, specificity and PPV were increased, though the increase was not significant.

This was due to the limitation of this study. Interleukin-6 (IL-6) is an early marker of sepsis which becomes positive even before the appearance of clinical features. As the newborn becomes symptomatic the level of IL-6 starts decreasing. To determine the significance of this marker ideally IL-6 levels should be tested hourly in order to detect the decreasing trend.

Moreover till now studies have not able to define any specific normal range for IL-6 for a particular geographic area.

In conclusion this study has limitations and more work is required in this field to make IL-6 a part of routine neonatal septic screening.

Conflict of Interest: None.

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