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Original Article

Paediatrics Section

A Prospective Study to Compare the Diagnostic Value of Serum Procalcitonin and CRP in Early Onset Sepsis

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ABSTRACT

Introduction: Neonatal sepsis is the most common cause of death in newborns in developing countries. Prompt diagnosis is the critical determinant in its outcome. As manifestations are often vague, clinically it is difficult to differentiate sepsis from non-infective conditions. Timely diagnosis is important as delay in initiation of antimicrobials can prove fatal. On the other hand empirical use of antibiotics not only increases the risk of antibiotic resistance but also delays the diagnosis of true condition. Procalcitonin (PCT) has been well evaluated in late onset sepsis but data pertaining to Early Onset Sepsis (EOS) are still lacking. We compared the diagnostic value of PCT and CRP (C-Reactive Protein) in EOS.

Aim: To compare the diagnostic value of serum PCT and CRP in early onset sepsis.

Materials and Methods: It was a prospective observational study conducted in Neonatal Intensive Care Unit of the Department of Paediatrics, Dr.S.N. Medical College, Jodhpur, India. All neonates delivered in hospitals attached to this medical college or referred here within 7 days of life and having ≥2 perinatal risk factors for sepsis or displaying clinical sepsis were included in the study. All enrolled neonates were subjected to sepsis screen, PCT levels and blood culture at birth or admission which ever was the earliest. PCT levels ≥ 0.5 ng/mL and CRP levels above 8mg/l were considered positive for EOS.

Results: Sensitivity and negative predictive value of PCT were higher than CRP (90.12% vs. 50.62% and 93.33% vs. 79.06% respectively). Also it had a higher positive predictive value of 40.56% than CRP where it was 37.61%. CRP was more specific (68.95% vs. 51.4%) with overall higher diagnostic accuracy (0.64 vs. 0.61) in comparison to PCT.

Conclusion: PCT is more sensitive and has a higher negative predictive value than CRP in early onset sepsis. Higher positive predictive value and specificity of CRP suggest that, PCT should not be used alone rather should be supplemented with CRP to correctly identify early onset neonatal sepsis.

Keywords: Acute phase reactant, Diagnostic accuracy, Neonatal sepsis, Sensitivity

CASE REPORT

Neonatal Sepsis is the most common cause of death in newborns in developing countries. It accounts for 25% of 4 million total neonatal deaths each year globally [1]. The incidence of neonatal sepsis among intramural babies has been reported as 30 per 1000 live births in 18 major hospitals across India (NNPD- National Neonatal-Perinatal Database) [2].

On the basis of source of causative organisms, neonatal sepsis has been classified as early and late onset. Majority of newborns with early onset infection present within the first day of life, fewer on the 2nd day and a smaller percentage between 48 hours and 6 days of life. As manifestations are often vague, clinically it is difficult to differentiate sepsis from non-infective conditions [3]. Timely diagnosis is important as delay in initiation of antimicrobials can prove fatal. On the other hand, empirical use of antibiotics not only increases the risk of antibiotic resistance but delays the diagnosis of true condition also.

Confirmation of sepsis requires isolation of bacteria from blood, or CSF or from any other sterile body fluids. But the rate of bacterial isolation is very low, and it takes time too [4]. CRP has been used for a long time to exclude sepsis because of its excellent negative predictive value. But it can be non-specifically raised in other conditions also [5]. Over reliance on CRP tends to over-diagnose sepsis.

To overcome it, other newer markers like PCT, Interleukin (IL) -6, IL-8, tumour necrosis factor alpha, resistin and visfatin are being studied [6-10]. Out of these, PCT seems to be most promising because of easy availability and cheaper cost. PCT has been well studied in late onset sepsis, but data regarding

its use in early neonatal sepsis are scarce. Present study was aimed to compare diagnostic value of PCT and CRP in EOS.

MATERIALS AND METHODS

This prospective observational study conducted on 300 newborns in Neonatal Care Unit of Paediatrics, Department at Dr. SN Medical College Jodhpur, India, over a period of one year extending from January 2016 to December 2016. Written informed consent was obtained from the parents of all the participant neonates. The study was approved by Institutional ethics committee.

All the newborns delivered in Umaid/MDM Hospital or referred here within 7 days of life and having ≥2 risk perinatal factors for sepsis or displaying clinical sepsis were included. Those who had, APGAR score less than 8, or congenital malformations, or suspected metabolic disorders were excluded.

Seven conditions were considered risk factors for sepsis: prematurity; febrile illness in the mother within two weeks of delivery; foul smelling/meconium stained liquor; prolonged rupture of membrane for>18 hours; single unclean or more than 3 clean vaginal examinations; prolonged labor>24 hours; difficult delivery with instrumentation or birth asphyxia.

Presence of following features were considered under clinical sepsis category: Neurological (convulsions, irritability, drowsiness, abnormal Moro's reflex, decreased activity, bulging fontanels); Respiratory (respiratory rate >60/min, grunting, apnoea, chest in drawing, central cyanosis); Cardiovascular (capillary refill time more than 3 seconds, rapid and weak pulse, pallor, mottling, bradycardia and tachycardia); Skin (pustules, petechiae, periumblical erythema or purulent discharge, deep jaundice); Temperature instability (temperature>99.9^0 F or <95.9^0 F); Renal impairment (decreased urine output, edema); poor feeding.

All enrolled neonates were subjected to blood cell count, CRP test, PCT levels and blood culture at birth or admission which ever was earliest, prior to introduction of antibiotics. Only those showing positive blood culture were considered to have proven sepsis. Parameters of diagnostic accuracy between PCT and CRP were compared.

Sample size calculation: Keeping sensitivity 1, specificity 0.25 and prevalence 0.28 (on the basis of results of previous study), 12 precision errors 0.06 and confidence interval of 95 %, sample size was calculated to be 280 babies. We enrolled total 300 neonates.

STATISTICAL ANALYSIS

All the data collected were transferred in to the Microsoft excel sheet and were analyzed using SPSS version 16. Quantitative data were expressed as mean±standard deviation and were compared using Student's 't'-test. Qualitative data were expressed as percentages/proportion and were analyzed by Chi-square test.

RESULTS

Mean birth weight, gestational age and age at admission of the 81 newborns with confirm sepsis were 2.0679±0.71533 kg, 34.827±2.597 weeks and 2.037±1.3825 days respectively. Males outnumbered females with a sex ratio of 1.38:1. Overall,180/300 (60%) neonates had elevated PCT levels (≥0.5 ng/mL) and 109/300 (36.33%) had positive CRP. Total 81/300 (27%) newborns had proven sepsis (blood culture positive), in rest of the cases 219/300 (73%) either blood was sterile or showed contaminants [Table/Fig-1].

In proven sepsis group, 41 (50.61%) were CRP positive and 73 (90.12%) were PCT positive [Table/Fig-2]. Sensitivity and negative predictive value of PCT were higher than CRP (90.12% vs. 50.62% and 93.33% V/s. 79.06% respectively). CRP was more specific (68.95% V/s. 51.4%) with overall higher diagnostic accuracy (0.64 V/s. 0.61) in comparison to PCT [Table/Fig-3].

Characteristics	Neonates with Proven Sepsis (n=81)	Neonates with Negative Blood Culture (n=219)	p-value
Birth weight (in kg)	2.0679±0.71533	2.145±0.733	0.4141
Gestational age (in weeks)	34.827±2.597	34.671±2.635	0.6482
Age at admission (in days)	2.037±1.3825	1.780±1.218	0.0964
Sex ratio	1.38:1	2.084:1	0.16

[Table/Fig-1]: Comparison of positive and negative blood culture groups.

	Blood Culture Positive (n=81)	Blood Culture Negative (n=219)	Total	p-value
CRP* positive	41	68	109	0.001758
PCT** positive	73	107	180	<0.0001

[Table/Fig-2]: CRP and PCT positivity in culture positive and negative groups.
*C-Reactive Protein, **Procalcitonin

Parameters	PCT	CRP
Sensitivity	90.12%	50.62%
Specificity	51.4%,	68.95%
PPV*	40.56%	37.61%
NPV**	93.33%	79.06%
PLR#	0.21	1.631
NLR##	1.69	0.720
Diagnostic accuracy	0.6166	0.64

[Table/Fig-3]: Comparison of diagnostic value of CRP and PCT.
*Positive predictive value, ** Negative predictive value, # Positive likelihood ratio, ## Negative likelihood ratio

DISCUSSION

CRP is the most commonly used acute phase reactant to diagnose and to monitor sepsis. It is produced by the hepatocytes in response to infection or tissue inflammation. In an acute phase reaction, its level rises rapidly within 2 hours and peaks within 48 hours. During resolution of inflammation, CRP declines slowly with a half-life of 18 hours [11]. But during sepsis rise of CRP level is comparatively slow, and thus has a low sensitivity early in the sepsis [12,13].

PCT is the precursor protein of calcitonin with no hormonal activity. This glycoprotein is normally produced by the C-cells of the thyroid gland [14]. In healthy persons its levels are undetectably low. In response to injection of bacterial endotoxins, its level rise rapidly within 6-8 hours, and reaches plateau between 12 and 48 hours [15]. The levels correlate with the severity of microbial invasion also.

During sepsis rise of CRP is 4-6 hours slower than PCT [15]. Similarly, after initiation of antibiotics PCT levels drop faster than CRP, with normalization of PCT levels after 5 days [16]. For these reasons PCT is considered better than CRP, and has been extensively evaluated in late onset sepsis. But it can be falsely elevated in early neonatal period, decreasing its utility in this entity [17]. In the present study we tried to explore the diagnostic potential of PCT in early onset sepsis by comparing it with CRP.

Diagnostic Value of CRP

In the present study, taking 8 mg/l as the cut off for CRP, its sensitivity, specificity, positive predictive value and negative predictive value were 50.62%, 68.95%, 79.06% and 37.61% with a diagnostic accuracy of 0.64. In previous studies sensitivity, specificity, PPV, and NPV ranged from 34.4% to 100%, 62.5% to 100%, 30% to 100% and 30% to 93.2% respectively. These variability in results could be because of different cut-off levels of CRP, different population (early onset sepsis, late onset sepsis, both early and late onset sepsis) and differences in criteria used to define sepsis (blood culture positive, sepsis screen positive or combination of these) [Table/Fig-4].

Study (year)	Sample size	Early(E)/Late onset sepsis(L)	Cut-off (mg/L)	Sensitivity (%)	Specificity (%)	NPV** (%)	PPV* (%)
Present study	300	E	8	50.62	68.95	37.61	79.06
Adib M et al., [10]	87	E+L	12	45	95	30	30
Thota U et al., [18]	85	E+L	6	34.4	62.5	32.25	77.78
In Ho et al., [19]	269	E	10	100	85.6	33.3	100
Naher et al., [20]	50	E+L	14	55	100	35.7	100
Mohsen AH et al., [21]	70	E	12	72.9	100	93.2	69.7

[Table/Fig-4]: Comparison of diagnostic value of CRP with previous studies.
*Positive predictive value, ** Negative predictive value

Author	Sample size	Cut-off (ng/mL)	Sensitivity (%)	Specificity (%)	PPV* (%)	NPV** (%)
Present study	300	≥0.5	90.12	51.14	40.56	93.33
Adib M et al., [10]	69	≥1.1	70	80	80	75
Thota U et al., [18]	85	≥0.5	89.60	78.57	65	93.6
Park IH et al., [19]	269	≥0.5	88.89	58.17	13.2	98.6
Mohsen AH et al., [21]	70	≥1.1	80	85.7	84.8	81.1

[Table/Fig-5]: Comparison of diagnostic value of PCT with previous studies.
*Positive predictive value, ** Negative predictive value

Author	Sensitivity (%)		Specificity (%)		PPV* (%)		NPV** (%)	
	PCT#	CRP##	PCT	CRP	PCT	CRP	PCT	CRP
Present study	90.12	50.62	51.14	68.95	40.56	79.06	93.33	37.61
Adib M et al., [10]	70	45	80	95	80	30	75	30
Thota U et al., [18]	89.60	34.4	78.57	62.5	65	77.78	93.6	32.25
Park IH et al., [19]	88.89	100	58.17	85.6	13.2	100	98.6	33.3
Naher et al., [20]	65	75	90	100	96.3	100	39.1	35.7
Mohsen AH et al., [21]	80	72.9	85.7	100	84.8	69.7	81.1	93.2

[Table/Fig-6]: Comparison between PCT and CRP in various studies.
*Positive predictive value, ** Negative predictive value,#C-Reactive Protein, ##Procalcitonin

Diagnostic Value of PCT

Sensitivity, specificity, positive predictive value and negative predictive value of PCT at ≥0.5 ng/mL in the present study were 90.12%, 51.14%, 40.56% and 93.33% respectively with a diagnostic accuracy of 0.6166. These findings are almost similar to the results of previous studies [Table/Fig-5].

Comparison of Diagnostic Value CRP and PCT

In the present study, sensitivity and negative predictive value of PCT were higher than CRP. These findings are in concurrence with the results of study of Thota U et al., [18] and Adib M et al., [10]. We found CRP to be more specific with higher positive predictive value, similar to the findings of Park IH et al., [19] and Naher BS et al., [20]. With regard to predictive values (both PPV and NPV), Mohseen AH et al., observed contrasting results [21] [Table/Fig-6].

LIMITATION

Firstly, unable to enrol the newborns with sepsis on day 1, so there was lack of uniformity. Specific cut-off values for each evaluation point over the first 48 hours of life were needed to improve the diagnostic accuracy of PCT as a marker for bacterial infection.

CONCLUSION

As a screening tool for early onset sepsis, PCT is better than CRP because of its higher negative predictive value and sensitivity. But PCT should not be used alone rather should be supplemented with CRP as it has a higher positive predictive value and specificity. Hence, to correctly identify early onset neonatal sepsis both CRP and PCT should be done.

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