Section: Pediatrics

Original Research Article

ROLE OF UMBILICAL CORD BLOOD PROCALCITONIN AS A BIOMARKER FOR PREDICTION OF EARLY NEONATAL SEPSIS

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Abstract

Background: Neonatal sepsis remains a critical concern, particularly in middle and lower-income countries, contributing significantly to infant morbidity and mortality. This study investigates the efficacy of umbilical cord blood procalcitonin (PCT) as a biomarker for early-onset sepsis in neonates, aiming to enhance diagnostic accuracy and facilitate timely intervention. Objective: To assess the diagnostic accuracy of cord blood Procalcitonin to predict Early onset neonatal sepsis (EONS). **Study Design:** It was a Prospective analytical case-control study. A total of 200 neonates between 28-42 weeks gestational age were included. Neonates admitted to NICU within the first 3 days of life with sepsis were taken as cases and neonates who did show any signs of sepsis were taken as controls. Umbilical cord blood samples were evaluated for PCT and C-reactive protein. Sensitivity, Specificity, and accuracy of PCT and CRP were calculated and compared. **Result:** Umbilical cord PCT levels were significantly elevated in neonates with proven sepsis, achieving a sensitivity of 94.4% and specificity of 86.9%, compared to CRP's lower metrics. The findings underscore the potential of cord blood PCT as a superior diagnostic tool for early-onset neonatal sepsis, which may lead to improved treatment outcomes by enabling prompt antibiotic therapy and reducing unnecessary treatments in non-infected infants. This study advocates for the incorporation of umbilical cord PCT testing into clinical practice to effectively address neonatal sepsis in resource-limited settings. **Conclusion:** Procalcitonin in cord blood is a promising biomarker to detect EONS with high diagn.ostic accuracy. Hence on the basis of results of our study, we recommend that a PCT- based algorithm must be made to initiate antibiotic therapy in susceptible neonates and also to decide on empirical antibiotic use for EONS depending upon the cord blood procalcitonin levels.

INTRODUCTION

Neonatal sepsis refers to an infection involving the bloodstream in newborns upto 4 weeks of age. It continues to remain a leading cause of morbidity and mortality among infants, especially in middle and lower-income countries despite the advancement in medical techniques and antibiotics.[1] It is divided into early-onset sepsis (EOS) or late-onset sepsis (LOS) based on the age of presentation after birth, with different experts using 72 hours or 7 days as the cutoff.

One of the reasons for same is delay in diagnosis of sepsis and therefore delay in initiation of antibiotics as a part of treatment. Hence there appears a need for biomarkers which could predict very well in advance the development of sepsis in a neonate before appearance of symptoms or clinical deterioration in a neonate.

In search of biomarkers to detect sepsis early, various haematological indices like white blood cell (WBC) count, absolute neutrophil count, immature/total neutrophil ratio and serological markers like high sensitivity C-reactive protein (hs-CRP) have been used for identification of at-risk babies but have low sensitivity.[2]

The Gold standard, blood cultures have risk of low yield / false negative results after especially if there is antenatal antibiotic exposure. Also, blood culture requires a substantiate amount of blood sample to give accurate results, which is again difficult to obtain in case of a neonate.[3] More so over the blood culture requires at least 48 hours to grow and show results. Additionally, in developing countries like India, blood culture testing facility is not available in

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most of the medical centres making it still more difficult to initiate early and specific treatment.[4]
Procalcitonin has recently established its efficacy as a marker for bacterial infections in both adult and Paediatric patients. Procalcitonin (PCT) level has been reported to increase in bacterial infections in newborns. However, there is also a physiological rise in PCT level in newborns during first 48–72 hrs of life.[5] Studies have found that PCT value in maternal serum or umbilical cord blood sample can help distinguish infected from healthy newborns.[3] Also, it is superior to WBC count and CRP values.[6]
Hence, evaluating cord blood PCT will lead to increased diagnostic accuracy as it avoids confounding factors like physiological rise of PCT following birth and PCT rise due to perinatal events like perinatal asphyxia, respiratory distress, hypoxic ischemia, pneumothorax or any intracranial bleed as shown in multiple previous studies.[7]
We in our research want to study the role of umbilical cord blood in predicting evidence of early onset neonatal sepsis so that appropriate timely measures can be taken and the morbidity and mortality could be decreased.
all neonates between the gestational age of 28-42 weeks delivered in our centre were taken as study population and umbilical cord blood was collected from all patients.
neonates <28 weeks, with fatal congenital anomalies, perinatal asphyxia, congenital heart diseases or any other acute surgical emergency were excluded from the study.
Neonates who got admitted in NICU within first 3 days of life with any evidence of sepsis (either a positive sepsis screen, or a positive blood or CSF culture or clinical signs and symptoms of sepsis without a positive sepsis screen) were included as cases and neonates who did not get admitted in NICU in next 7 days were taken as controls.
Proven sepsis was defined as positive clinical signs and symptoms plus a positive bacteria culture (either blood or CSF). Probable sepsis was defined as a positive sepsis screen but with a negative culture and clinical sepsis as only clinical signs and symptoms suggestive of sepsis with negative bacterial culture and negative sepsis screen.
Informed consent was taken from parents of all neonates. Detailed medical and obstetric history, details of mode of delivery, intrapartum details, resuscitation details and general physical examination findings at time of birth were noted in a proforma.
Within 2 min of birth of the baby but before the delivery of placenta, umbilical cord blood sample was taken after clamping the cord from placental end on two sides. The cord was cleaned by spirit and minimum 2ml of blood was drawn. Samples collected were immediately sent for sepsis screen and PCT.
Hs-CRP was done by the Beckman Coulter AU Analyzer while the PCT level of umbilical cord blood was measured by immune- lumino -assay method. A positive PCT value was defined as more than 0.5ng/ml and was further classified as 0.5-2ng/ml (weakly positive), 2-10 ng/ml (positive) and >10ng/ml (strongly positive). A positive CRP was defined as a value >0.6mg/dl.
SPSS 18 was used to analyse the data. T-test and Chi-Square tests were also used for quantitative and qualitative variables. A value of P <0.05 was considered significant.

MATERIALS AND METHODS

It was a prospective observational study.
All neonates between the gestational age of 28-42 weeks delivered in our centre were taken as study population and umbilical cord blood was collected from all patients. Neonates <28 weeks, with fatal congenital anomalies, perinatal asphyxia, congenital heart diseases or any other acute surgical emergency were excluded from the study.
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RESULTS

Out of the 200 neonates, there were 93 cases and 107 controls. 93 cases were subdivided into 3 subgroups -proven sepsis, probable sepsis and clinical sepsis. 42 neonates (45.1%) in the case group and 40(37.3%) in the control group were born by caesarean delivery. 47.3% in the case group and 44.8% in the control group were females. 51 neonates (54.8%) in the case group and 41(38.3%) in the control group had a gestational age <35 weeks. 54 neonates (58%) amongst cases had a birth weight of more than 2500 grams.

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Out of the 93 cases 18 had proven sepsis, 34 had probable sepsis and 41 had clinical sepsis. The PCT level of the umbilical cord was >0.5ng/ml in 17 (94.4%), 29(85.2%) and 20(48.7%) cases amongst the proven sepsis, probable sepsis and clinical sepsis groups respectively [Table 1]. Out of the 18 proven sepsis cases the most common organism grown was klebsiella (8 out of 18) followed by E. Coli (4), MR-CONS (3) and Acinetobacter (3). The CSF analysis in 17 of the 18 cases was normal while 1 case grew MR-CONS on CSF culture.

The sensitivity and specificity of umbilical cord PCT in proven sepsis group was 94.4% and 86.9% respectively. the same for probable sepsis group was 85.3% and 86.9%. overall, the umbilical cord PCT had a sensitivity of 70.97% and a specificity of 86.92% with a diagnostic accuracy of 95% in predicting the development of early onset neonatal sepsis against the 44.09% sensitivity and 65.42% specificity of CRP. On ROC curve the PCT curve had an AUC of 0.8 as compared to 0.55 for CRP indicating that Procalcitonin (PCT) is a more effective biomarker than C-reactive protein (CRP) for diagnosing early-onset neonatal sepsis, with higher sensitivity, specificity, and overall diagnostic accuracy [Figure 1].

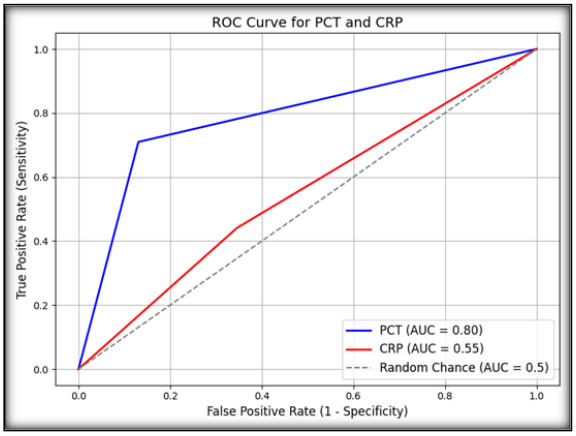

Figure 1

In the proven sepsis group 4(22.2%) had PCT between 0.5-2ng/ml, 10(55.5%) had a PCT between 2-10ng/ml and 3(16.6%) patients had PCT>10ng/ml. amongst the probable sepsis group, 11(32.3%) had PCT between 0.5-2ng/ml, 13(38.2%) had PCT between 2-10ng/ml and 5(14.7%) had a PCT>10ng/ml. in the clinical sepsis group 11(26.8%) had PCT between 0.5-2ng/ml, 5(12.1%) had a PCT value between 2-10ng/ml and 4(0.09%) had PCT >10ng/ml. More so ever clinically significant correlations were seen between birth weight, PCT and gestational age with all three subgroups of sepsis ($p=0.04$, $p<0.0001$ and $p<0.001$ respectively). A significant difference was also seen between CRP and the three sepsis subgroups ($p=0.049$) [Table 2].

The mean cord blood PCT among cases was 8.206±13.516 and the same for controls was 0.43±0.264. This difference was statistically significant ($p<0.001$). Moreover, the PCT mean based on mode of delivery and gestational age was significantly higher in the case group than in the control group ($p<0.001$)

In both case and control groups, there was a significant relationship between sepsis with mode of delivery and gestational age ($p<0.001$). However, there was no significant relationship between sepsis and neonate's gender ($p=0.23$). [Table 3].

Table 1: Diagnostic efficacy of different haematological parameters for prediction of neonatal sepsis.

Parameters	Proven Sepsis (18)	Probable Sepsis (34)	Clinical Sepsis (41)	Controls (107)
Cord Blood PCT 0.5	17	29	20	14
Blood CRP>0.6	13	9	19	37

Table 2: Cases based on gender, birth weight, mode of delivery, procalcitonin and CRP levels

		Proven sepsis	Probable sepsis	Clinical sepsis	P value
Gender	Male	12	19	18	0.56
	Female	6	15	23	
Birth weight	>2.5kg	4	13	22	0.04
	<2.5 kg	14	21	19	
Mode of delivery	Vaginal	11	13	27	0.45
	Caesarean	7	21	14	
Procalcitonin levels	<0.5ng/ml	1	5	21	<0.0001
	0.5-2ng/ml	4	11	11	
	2-10ng/ml	10	13	5	
	>10ng/ml	3	5	4	
CRP levels	0-6	8	13	31	0.049
	>6	10	21	10	
Gestation	<35 weeks	16	18	24	<0.001
	>35 weeks	2	16	17	

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Table 3: Mean pct levels in case and control groups based on mode of delivery, gestation and gender

		Case group	Control group	P value
Mode of delivery	Normal	10.08833±18.74	0.42+0.16	<0.001
	Caesarean	6.46+4.57	0.439+0.368	<0.001
Gestation	<35 weeks	9.33+17.52	0.452+0.386	0.006
	>35 weeks	6.75+4.53	0.417+0.158	<0.001
Gender	Male	5.85+ 13.89	0.42+0.112	0.019
	Female	0.62+0.588	0.43+0.303	0.23

DISCUSSION

Sepsis is one of the major causes of mortality in neonatal ICUs in developing countries despite the advancement in medical techniques and antibiotics.[4] Screening the cord blood for different biomarkers of sepsis like CRP, PCT, WBC counts might help the paediatricians to suspect neonates at risk of developing early onset sepsis and start treatment early. The current study demonstrated that the umbilical cord PCT levels in neonates with early onset neonatal sepsis were significantly higher than that in the control group. The present study also suggested that the PCT level of umbilical cord blood was significantly higher in the proven sepsis group than that in the other two subgroups of sepsis (probable and clinical). Similar results were obtained in a study done by Lopez et al.[8]

Our study on 200 neonates found that umbilical cord Procalcitonin (PCT) is a more effective biomarker than C-reactive protein (CRP) for diagnosing early-onset neonatal sepsis, with higher sensitivity, specificity, and overall diagnostic accuracy. Other studies done on umbilical cord blood PCT have shown similar results for predicting development of early onset neonatal sepsis.[9,10] The present study found that the sensitivity and specificity of umbilical cord PCT in proven sepsis group was 94.4% and 86.9% respectively. The same for probable sepsis group was 85.3% and 86.9%. Overall, the umbilical cord PCT had a sensitivity of 70.97% and a specificity of 86.92% with a diagnostic accuracy of 95% in predicting the development of early onset neonatal sepsis against the 44.09% sensitivity and 65.42% specificity of CRP. Outcomes similar to our study were noted in a meta-analysis which concluded that CRP alone was not adequate enough for the diagnosis of Early onset neonatal sepsis and Umbilical cord blood PCT can be used as a valid test.[11] in contrast to our study, a study done by Patrick et al. found cord blood CRP to have sensitivity of 100% and specificity of 90%. The better diagnostic accuracy of PCT in our study could be because our study had a comparatively bigger sample size than Patric et al.

Also, our study showed that in both case and control groups, there was a significant relationship between sepsis with mode of delivery and gestational age ($p<0.001$).[12]

Limitation of our study was not taking maternal procalcitonin levels along with the umbilical cord blood which could have been reflected in neonate's cord blood. Our study concludes that the PCT level of umbilical cord blood in neonates with early sepsis was higher than that in those without evidence of sepsis. it had a higher sensitivity in the proven sepsis group. This finding supports the usefulness of the PCT level of the umbilical cord in the early diagnosis of early neonatal sepsis as PCT could assist in early start of antibiotic therapy in babies at high risk of infection and also decrease the antibiotic prescription in non-infected neonates.

CONCLUSION

Procalcitonin in cord blood is a promising biomarker to detect EONS with high diagn.ostic accuracy. Hence on the basis of results of our study, we recommend that a PCT- based algorithm must be made to initiate antibiotic therapy in susceptible neonates and also to decide on empirical antibiotic use for EONS depending upon the cord blood procalcitonin levels.

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