Comparison of Procalcitonin Versus C Reactive Protein in The Detection of Neonatal Sepsis

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ABSTRACT

Objective: To compare procalcitonin and C-reactive protein in the detection of neonatal sepsis keeping blood culture as gold standard.

Study Design: Cross sectional study.

Place and Duration of Study: Neonatal Intensive Care Unit, Children Hospital, Pakistan Institute of Medical Sciences, Islamabad, from Jul to Dec 2018.

Methodology: Neonates up to 28 days of age with the suspicion of sepsis were selected. All the patients with congenital malformation were excluded. Two bed-sided tests i.e., procalcitonin and C-reactive protein was performed using standardized laboratory methods. The diagnostic strength of both tests was compared.

Results: A total of 154 neonates were enrolled in this study. Male neonates were dominant in this study 95 (61.7%). The mean age of patients was 6.1 ± 3.8 days. C reactive protein had a sensitivity and specificity of 50.9% and 28.7% respectively. While procalcitonin was found to have a comparatively high sensitivity and specificity 73.6% and 38.6% respectively. On blood culture test; klebsiella pneumoniae, pseudomonas, staphylococcus aureus were found out to be the most common pathogens.

Conclusion: Procalcitonin has a better sensitivity and specificity than C reactive protein in the diagnosis of early neonatal sepsis.

Keywords: C-reactive protein, Early diagnosis, Neonatal sepsis, Procalcitonin.

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INTRODUCTION

Neonatal sepsis (NNS) is a leading cause of morbidity and mortality in newborns.[1] NNS is characterized by systemic signs/symptoms and bacteraemia during the first 28 days of life. NNS is one of the main reasons for admissions in the neonatal intensive care units worldwide.[2] Globally the trend of decrease in the deaths in neonatal age, is way slower than those in post neonatal periods (47% versus 58%). Overall globally neonatal deaths decreased from 36/1000 live births to 19/1000 live births between 1990 and 2015. However, consistent mortality rates are continuously haunting many developing countries, specially, Pakistan where no progress has been made in this endeavor.[3]

Early diagnosis of sepsis leads to targeted therapy and has good recovery rates. The early signs and symptoms are mostly non-specific and can easily be mixed up with the non-infective causes. Non-specific signs/symptoms make it very challenging to formulate a timely clinical diagnosis.[4] On the other hand based on the clinical symptoms only the initiation of antibiotics may lead to unnecessary treatment and consequently antimicrobial resistance.

The gold standard diagnostic tool for the sepsis is blood culture, however, due to its late outcome; patients lose 72 hours of intervention period. Though culture gives a very accurate diagnosis of infection, the time it takes can put a case to unnecessary delays and risks. The neonatal physicians are always looking for an early diagnostic tool for sepsis so that time loss could be prevented and the chances of severe morbidity and mortality could be avoided.[5]

Procalcitonin (PCT) has recently been introduced as a bedside test in our local settings which can help detect the disease in the initial stages and can give physicians an opportunity to streamline adequate therapeutic regimens in the management of sepsis, which can also help in reducing Antimicrobial resistance (AMR). It is a helpful tool in antibiotic stewardship. Though PCT is costly than C-reactive protein (CRP), the treatment and hospitalization costs associated with NNS are far more and the physical and mental stress faced by parents is immense. PCT has been shown to be highly sensitive marker of early neonatal sepsis.[6] Similarly, CRP also shows better strength with different cutoff levels but the overall low sensitivity for the

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detection of early neonatal sepsis is a limitation of this test.[7,8]

Previous evidence reveals PCT sensitivity in the early diagnosis of neonatal sepsis ranging between 83-100%.[9] A recent study by Adib *et al*, witnessed that PCT has sensitivity of 70%, specificity 80%, PPV 80% and NPV of 75% in diagnosing early onset neonatal sepsis. The confirmed cases of sepsis on the basis of blood culture were 29.8% in their study.[7]

There was little recorded scientific evidence on PCT from Pakistan. The objective of this study was to compare the diagnostic accuracy of PCT with that of CRP in detecting early neonatal sepsis keeping blood culture as gold standard.

METHODOLOGY

A cross sectional study was conducted at the Neonatal Intensive Care Unit in the Department of Neonatology, Children Hospital, Pakistan Institute of Medical Sciences, Islamabad, from July to December 2018, in which 154 neonates with the suspicion of sepsis were enrolled. The study was initiated after getting approval from the Hospital Ethics Committee and written informed consent was taken from parents or guardians.

Inclusion Criteria: Neonates (0-28 days) admitted in the NICU with any two to three clinical signs/symptoms indicative of probable sepsis (maternal fever, newborn's feeding intolerance, lethargy, febrile, respiratory distress, apnea, seizures, tachypnea, bradycardia, abdominal distension or vomiting) were included in the study.

Exclusion Criteria: The neonates coming with the proven sepsis and referred from other healthcare facilities, those with a congenital malformation were excluded from the study.

The sample size was based on the previous diagnostic evidence on procalcitonin, sensitivity of 75% and specificity of 95%[10] and using anticipated prevalence of NNS based on blood culture 28.9%.[6] The calculated sample came out to be 154. Non-probability convenient sampling was used for the enrollment of this study.

The neonates with clinical symptoms of sepsis warranted the septic screening. Before any intervention with antibiotics, blood samples for blood culture (1-2 ml), PCT and CRP measurement (1-2 ml) were obtained by peripheral venous puncture. Serum was separated by centrifugation and stored in two plastic tubes for the measurements. The confirmation of neonatal sepsis was based on blood culture test. Therapy was initiated based on the findings of PCT and CRP investigations.

The demographic and clinical details of patients were noted on the structured proforma specifically designed for the study. The findings of PCT and CRP were noted. After 48-72-hours initial report of blood culture and on 7th day the confirmation with blood culture were noted. The standardized hospital protocol for neonates with sepsis was followed.

PCT is a one-step in vitro diagnostic test based on immunochromatography. The device and specimen were kept in room temperature of 18-30^{o}C or 64-86^{o}F) before testing. Sample was obtained using suitable micro-pipette equipped with fresh pipette tip. By pressing the 'test' button of HUBI-QUAN pro and waiting for 15 minutes results were obtained. The cut off level of >1.1 ng/l was taken as positive PCT result.[9]

CRP is designed to measure the concentration of protein in human blood and shows the test results in quantitative base. The sample was inserted in the device (HUBI-QUAN pro), 100 ul of diluted specimen (buffer contained blood) inserted in specimen hole and by pressing 'test' button and waiting for 5 minutes, the result was generated. The cut off level of >10 mg/dl was taken as positive CRP.[10]

All the study procedures and data collection was performed by the principal investigator, so that selection bias can be averted and data quality could be maintained. The final outcome was measured in terms of diagnostic accuracy of PCT and CRP in neonatal sepsis. The diagnostic measurements were sensitivity, specificity, PPV and NPV calculated using standardized formulae available for measuring for diagnostic accuracy.

Data were analyzed by using SPSS version 22. The quantitative variables like age, CRP, procalcitonin were measured as mean and standard deviations. The categorical variables like gender, clinical features, CRP findings, procalcitonin findings, blood culture findings and pathogen type were measured as frequency and percentages. The two by two table was generated, to find out the values of true positive, false positive, false negative and true negatives. Based on the values of TP, FP, FN and TN and using standardized formulae the diagnostic accuracy parameters of sensitivity, specificity, PPV and NPV were calculated.

RESULTS

In this study, the primary outcome was the comparison of diagnostic strength of CRP and procalcito-

nin in diagnosing sepsis keeping blood culture as gold standard. Most of the neonates presented in the first 7 days of life 102 (66.2%). The mean age of patients was 6.1 ± 3.8 days. Male gender was predominant 95 (61.7%). When the maternal characteristics of patients were assessed, chorioamniotitis was present in 3 (1.9%) patients and pre-rupture of membrane >24 hours was present in 7 (4.5%) cases. Almost one-third neonates 47 (30.5%) had low birth weight and 56 (36.1%) were premature. Respiratory distress was seen in 41 (26.6%) cases, whereas lethargy 27 (17.5%), tachypnea 35 (22.7%) and feeding intolerance 21 (13.6%) were the other frequent clinical complaints noted in study patients. Further details regarding baseline characteristics were shown in Table-I.

Table-I: Baseline characteristics of the patients (n=154).

Demographic Characteristic	n (%)
Age (days)	
Up to 6	102 (66.2%)
7-13	46 (29.9%)
14 or above	6 (3.9%)
Mean ± SD	6.1 ± 3.8 years
Gender	
Male	95 (61.7%)
Female	59 (38.3%)
Maternal Clinical Features	
Fever	-
Chorioamnionitis	3 (1.9%)
PROM >24 hours	7 (4.5%)
Neonatal Clinical Features	
Low birth weight	47 (30.5%)
Prematurity	56 (36.1%)
Lethargic	27 (17.5%)
Respiratory distress	41 (26.6%)
Feeding intolerance	21 (13.6%)
Seizures	10 (6.5%)
Tachypnoea	35 (22.7%)
Abdominal distension	15 (9.7%)
Bradycardia	3 (1.9%)

The findings of C reactive protein and procalcitonin were compared according to blood culture findings, it was found out that 27 (50.9%) CRP positive cases (true positive) were also found positive by blood culture whereas 26 (49.1%) of CRP negatives (false negative) were actually positive as confirmed by blood culture. Similarly, 39 (73.6%) of procalcitonin cases were also found positive by blood culture (true positive), whereas 14 (26.4%) cases proven negative by PCT were actually positive on blood culture (false negative). The difference in true positive cases between CRP and PCT was statistically significant (Table-II).

Table-II: Comparison of c reactive protein and procalcitonin findings with blood culture results in the study (n=154).

	Blood Culture	
	Positive (n=53)	Negative (n=101)
C-Reactive Protein		
Positive	27 (50.9%)	72 (71.3%)
Negative	26 (49.1%)	29 (28.7%)
Procalcitonin		
Positive	39 (73.6%)	62 (61.4%)
Negative	14 (26.4%)	39 (38.6%)

The most common pathogen was *klebsiella pneumoniae* seen in 16 (10.3%) study cases, followed by pseudomonas 14 (9.1%), *staphylococcus aureus* 14 (9.1%) and *E-coli* found in 9 (5.8%) cases. Other details regarding pathogens were presented in Table-III.

Table III: The bacterial pathogens found in study patients (n=154).

	n (%)
Klebsiella Pneumonia	16 (10.3%)
Pseudomonas	14 (9.1%)
Staphylococcus Aureus	14 (9.1%)
Escherichia Coli	9 (5.8%)
Strep. Pneumonia	2 (1.2%)

It was noticed that CRP had a sensitivity and specificity of 50.9% and 28.7% respectively, whereas PCT was found to have a comparatively high sensitivity and specificity 73.6% and 38.6% respectively. One interpretation could be that CRP had an average level of sensitivity in diagnosing neonatal sepsis whereas PCT had a significantly higher sensitivity in detecting early onset of NNS. The overall diagnostic accuracy was also found reasonably high in PCT than CRP (50.6% versus 36.3%) (Table-IV).

Table-IV: Diagnostic parameters of C-reactive protein and procalcitonin in the diagnosis of neonatal sepsis keeping as blood culture gold standard.

Diagnostic Parameters	Values
C-reactive Protein	
Sensitivity (TP/TP+FN)	50.9%
Specificity (TN/TN+FP)	28.7%
PPV (TP/TP+FP)	27.3%
NPV (TN/TN+FN)	52.7%
Diagnostic Accuracy (TP+TN/Total patients)	36.3%
Procalcitonin	
Sensitivity (TP/TP+FN)	73.6%
Specificity (TN/TN+FP)	38.6%
PPV (TP/TP+FP)	38.6%
NPV (TN/TN+FN)	73.6%
Diagnostic accuracy (TP+TN/Total patients)	50.6%

DISCUSSION

This study validates the previous evidence that procalcitonin is highly accurate in detecting early onset of neonatal sepsis and is a better marker than CRP test.[11,12] Neonatal mortality is very high in Pakistan, with sepsis being the main cause. PCT as a bedside diagnostic option, can save lives, save physicians' time, financial costs related to burden on the healthcare setting and individual psychological pressures and financial costs related to long hospital stays.[10,11] Though our findings regarding the sensitivity of PCT and CRP (73.6% and 50.9%) were comparable to the previous studies, the specificity (38.6% and 28.7% respectively) has been seen comparatively low. A similar validity of CRP and Procalcitonin was reported by Adib *et al*, from Iran where they found sensitivity of 45% and 70% respectively, however, their specificity was significantly higher than our findings.[7] Many other studies have also reported a high sensitivity of PCT compared to CRP in detecting neonatal sepsis.[6,10] A previous study by Dollner *et al*, witnessed a fair to average level of sensitivity and specificity of CRP.[13] Chacha *et al*, found an average level sensitivity while high specificity of CRP.[1] A local study by Janjua *et al*, witnessed an even low sensitivity and specificity using a lower CRP cutoff level.[14]

Though majority of the data on the diagnostic strength of PCT and CRP clearly reveal superiority of the former, there are some reports which witnessed a similarity. Mahale *et al*, concluded that PCT and CRP are reliable markers which aid in the early diagnosis of neonatal sepsis and both have the same diagnostic accuracy.[15] Chin *et al*, reported a sensitivity of 69.5% and specificity of 64.5% for PCT, compared to 67.25% of sensitivity and 93.9% of specificity for CRP.[16] Similarly, Janota *et al*, indicated sensitivity and specificity in the range of 75% and 59% for procalcitonin respectively.[17] It can be noticed that majority of the previous evidence shows superiority of PCT when compared with CRP. Though there are differences in the cost, as CRP is much cheaper but its validity is low and the high sensitivity of PCT makes it ideal for early diagnosis and opens ways for management of neonatal sepsis.

The common pathogens in our study were *klebsiella pneumonia* (9.7%), followed by *streptococci* (6.4%), *strep. pneumonia* (5.8%) and *H. influenza* (5.1%). Adib *et al*, found *staphylococcus aureus*, *streptococcus* and *E.coli* as most common pathogens in their patients.[7] A study by Hoogen *et al*, witnessed *staphylococcus, streptococcus, klebsiella* and candida as most common pathogens.[18] Mahale *et al*, found *klebsiella* and *E.coli* as the most common pathogens in their series of patients.[15] The evidence regarding identification of bacterial pathogens vary from region to region and also depends upon the social norms of the specific community.

Pakistan being an over populated country with majority of the community belonging to poor socioeconomic class, the already burdened health settings need a rapid system for screening of suspected sepsis so that timely management with adequate drugs can be initiated. Thus, keeping our national social and demographic demands the current study findings have a beneficial result suggesting that PCT can be utilized as a bedside test for detecting neonatal sepsis.

Procalcitonin has a better sensitivity and specificity than CRP in the diagnosis of early neonatal sepsis. Procalcitonin can be utilized as a first line diagnostic option so that patients' lives and physicians' time could be saved as well as financial costs related to the burden on healthcare settings could be curtailed. Further large-scale studies are needed to assess the diagnostic benefits of these tests in terms of management outcome.

CONCLUSION

Procalcitonin has a better sensitivity and specificity than C reactive protein in the diagnosis of early neonatal sepsis.

Conflict of Interest: None.

Authors' Contribution

WA: Basic idea and design of study, writing manuscript, HS: Basic idea and design of study, and critical review, SG: Data analysis and interpretation, AH: Data Collection, QUA: Litrature review, QZ: Proof reading.

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