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DIAGNOSTIC ACCURACY OF PROCALCITONIN FOR DIAGNOSING NEONATAL SEPSIS KEEPING BLOOD CULTURE AS GOLD STANDARD

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Abstract

Background: *Neonatal infections contribute to third most common cause of neonatal deaths in developing parts of the world. This study was planned to determine diagnostic accuracy of procalcitonin for diagnosing neonatal sepsis taking blood culture as gold standard.*

Subjects and Methods: *This cross-sectional validation study was performed at the Pediatric Medicine Department of The Children's Hospital and Institute of Child Health Multan, from 17th February 2024 to 16th August 2024. Consecutive 195 neonates of either gender presenting with suspected sepsis were enrolled after parental informed consent. Probable neonatal sepsis was defined by positivity in at least 2/5 criteria: low total leukocyte count, low absolute neutrophil count, an immature-to-total neutrophil ratio ≥0.2, elevated ESR, or raised C-reactive protein. Confirmed sepsis required isolation of a pathogenic organism from blood, urine, or cerebrospinal fluid as definitive evidence. Serum procalcitonin was measured by immunoluminometry and cut off levels for sepsis were set at ≥0.5 ng/ml. Diagnostic accuracy of procalcitonin is calculated against probable and culture confirmed neonatal sepsis.*

Results: *Median neonatal age was 13 days, with 56.9% being male. Probable sepsis was diagnosed in 64.1% of cases, while 54.9% were confirmed by culture. Serum procalcitonin demonstrated moderate sensitivity (57.6%, 51.4%) paired with high specificity (98.6%, 79.6%) and an excellent positive predictive value (98.6%, 75.3%) for probable and confirmed neonatal sepsis respectively.*

Conclusion: *Although a serum procalcitonin level of ≥0.5 ng/mL is highly specific for neonatal sepsis, its limited sensitivity indicates that additional diagnostic markers are necessary for early detection and optimal clinical management.*

INTRODUCTION

In underdeveloped countries, neonatal sepsis accounts for 30–50% of all newborn deaths, making it the most common cause of infant mortality. According to estimates, sepsis affects 20% of

newborns.[2] During the first 28 days of life, a systemic bacterial infection can cause the clinical condition known as neonatal septicaemia.[3] There are two types of neonatal sepsis: early onset and late onset.[3] It can occasionally be challenging to diagnose infection in neonates based only on physical findings because symptoms are not always present and can be vague.[4] Blood cultures, which require at least 48 to 72 hours and only produce a positive response in 10–60% of cases, are the basis for the definitive diagnosis of newborn sepsis.[5]

Neonatal sepsis can be accurately diagnosed using the C-reactive protein (CRP) marker. The liver produces CRP, the most widely utilized acute phase reactant.[6] However, the CRP levels increase 12–24 hours after infection and is high for 3–7 days.[6] In recent years, a number of blood biomarkers that may be used to diagnosis systemic and local infections have been discovered. Thyroid gland cells generally secrete procalcitonin (PCT), which is a 116 amino acid that forms calcitonin. However, in cases of sepsis, me, nervous system and lung infections, and urinary tract infections, the amount of PCT may rise. Prior to the increase in CRP, there was an increase in procalcitonin (PCT).[7,8]

In a study by Akter J et al, 75 newborns with suspected septicemia were enrolled. Neonates who had clinical sepsis were 50.7% and confirmed sepsis was seen in 49% cases. The increased level of procalcitonin was present in 48% newborns with confirmed sepsis and 23.7% newborns who were clinically suspected of sepsis. At a cut-off limit of >500pg/ml, the sensitivity of PCT to detect septicemia was 48.6%, specificity 76.3%, positive predictive value (PPV) was 66.7%, and negative predictive value (NPV) was 60.4%.[9] Chowdhury MSH et al included a total 55 newborns with suspected sepsis. Proven sepsis was seen in 49.09% and clinical sepsis in 50.9% cases. The increased PCT was present in 48% newborn with confirmed sepsis and clinical symptoms of sepsis were present in 25% newborn. At a cut-off value > 500pg/ml, the sensitivity, specificity, PPV and NPV of procalcitonin in detecting sepsis was 46.4%, 75%, 67.9%, and 60.7%.[10]

The classical feature is that PCT increases in infections which involve bacteria and fungi but remains normal in inflammations and infections involving viruses. Therefore, this study has been planned in our local setting to identify the accuracy of PCT to diagnose neonatal sepsis. The measurement of procalcitonin if found reliable, will be utilized for timely diagnosis of sepsis in newborns so that the condition would be treated immediately without any delay.

SUBJECTS AND METHODS

This cross-sectional validation study was executed at Pediatric Medicine department of The Children's Hospital and Institute of Child Health Multan over a period of six months from 17th February 2024 to 16th August 2024, after obtaining approval from the institutional ethical review committee approval (No: 124/CH&ICH Multan, dated: 18-01-2024). Neonates 1 – 28 days of life, either male or female gender and suspected cases of sepsis were enrolled in the study consecutively after parental informed consent. Neonates with perinatal asphyxia, congenital abnormalities, meconium aspiration, ABO / RH – isoimmunization and antibiotic use before admission were excluded from the study.

A neonate was suspected with sepsis if both the risk factors and clinical features were present. The risk factors included any one or more of maternal history of febrile illness (T ≥ 101^0 F) in 72 hours before delivery, liquor with bad odor, membranes rupture for more than 24 hours. Clinical features included symptoms of poor cry, inability to suck, lethargy and signs of temperature variations (> 100.5^0F or < 96^0F), capillary refill time >3 seconds, decreased tone, diminished neonatal reflexes, breathing rate > 60/minute, apnea and gasping breathing and heart rate < 80/minute (bradycardia) or > 160/minute (tachycardia). Suspected cases underwent septic screen in the form of complete blood counts, micro-ESR, C-reactive protein (CRP), blood / urine / CSF cultures and serum procalcitonin levels.

Neonatal sepsis was labelled probable if ≥ 2 out of the 5 parameters were positive i.e. total leukocyte count (TLC) <5000/mm^3, absolute neutrophil count <1800/mm^3, immature to total neutrophil ratio ≥0.2, Micro-ESR of 3+ age in days in first 7 days of life, CRP >6mg/dL). Probable neonatal sepsis will be confirmed if pure growth of a pathogenic organism is obtained from the blood, urine or cerebrospinal fluid. The serum PCT levels were checked on admission by quantitative immunoluminometry method by use of

Lumitest kit. In this assay, a PCT value of ≥0.5 ng/ ml was suggestive of neonatal sepsis.

The sample size for this study was calculated by use of formula for one-sample sensitivity and specificity at https://wnarifin.github.io/ssc/sssnsp.html. Based on previously reported data, the frequency of culture-proven neonatal sepsis was estimated at 49.3%. The sensitivity and specificity of procalcitonin (PCT) to diagnose neonatal sepsis were assumed to be 48.6% and 76.3%, respectively.[9] Using an absolute precision of 10% and a 95% confidence level, the minimum required sample size was calculated to be 195 neonates. The data was analyzed through SPSS version 23. Descriptive statistics are reported as mean ± SD for numerical and frequency and percentages for categorical data. 2 x 2 contingency table was constructed taking definite and probable sepsis as gold standard and diagnostic accuracy of PCT was calculated in terms of sensitivity, specificity, PPV, NPV, accuracy and positive and negative likelihood ratios with 95 % confidence interval.

RESULTS

The median (IQR) age of the neonates was 13 (9) days and 56.9% (n=111) were males. The mean gestational age at delivery was 36.9 ± 2.1 weeks and 66.7% were delivered at term through SVD in 63.1% (n=123) of cases. In 64.1% (n=125) of the cases sepsis was labelled as probable and sepsis was indicated by procalcitonin levels (>0.5 ng/ml) in 37.4% (n=73) and was confirmed on blood culture in 54.9% (n=107) of the cases **[Table 1].**

Table 1: Characteristics of neonates with suspected sepsis (N=195)	
Age (days)	13 (9)
Gestational Age (weeks)	36.9 ± 2.1
Weight (kg)	2.5 ± 0.8
Gender	
Male	111 (56.9)
Female	84 (43.1)
Delivery	
Term	130 (66.7)
Preterm	65 (33.3)
Mode of delivery	
SVD	123 (63.1)
C-section	72 (36.9)
Serum Procalcitonin levels (ng/ml)	0.4 (2.4)
Probable Sepsis (Yes)	125 (64.1)
Sepsis on Procalcitonin (> 0.5 ng/ml)	73 (37.4)
Blood culture confirmed sepsis (yes)	107 (54.9)

Diagnostic accuracy of serum PCT (≥ 0.5ng/ml) to diagnose probable neonatal sepsis in shown in **Table 2**.

Table 2: Diagnostic accuracy of serum procalcitonin levels for probable sepsis in neonates with suspected sepsis (N=195)		
Sepsis based on Procalcitonin levels	**Probable Sepsis**	
	Yes	**No**
Yes	72	1
No	53	69
Sensitivity	57.6% (95% CI: 48.4% to 66.4%)	
Specificity	98.6% (95% CI: 92.3% to 99.9%)	
Positive predictive value	98.6% (95% CI: 91.1% to 99.8%)	

Negative predictive value	56.6% (95% CI: 51.4% to 61.5%)
Accuracy	72.3% (95% CI: 65.5% to 78.5%)
Positive likelihood ratio	40.3 (95% CI: 5.73 to 283.89)
Negative likelihood ratio	0.4 (95% CI: 0.35 to 0.53)

Diagnostic accuracy of serum procalcitonin (≥ 0.5ng/ml) for confirmed neonatal sepsis in shown in **Table 3**.

Table 3: Diagnostic accuracy of serum procalcitonin levels for blood culture confirmed sepsis in neonates with suspected sepsis (N=195)

Sepsis based on Procalcitonin levels	**Confirmed Sepsis**	
	Yes	**No**
Yes	55	18
No	52	70
Sensitivity	51.4% (95% CI: 41.5% to 61.2%)	
Specificity	79.6% (95% CI: 69.6% to 87.4%)	
Positive predictive value	75.3% (95% CI: 66.1% to 82.8%)	
Negative predictive value	57.4% (95% CI: 51.9% to 62.7%)	
Accuracy	64.1% (95% CI: 56.9% to 70.8%)	
Positive likelihood ratio	2.51 (95% CI: 1.60 to 3.95)	
Negative likelihood ratio	0.61 (95% CI: 0.49 to 0.76)	

DISCUSSION

With its high death rate, neonatal sepsis continues to be difficult for neonatal healthcare professionals to diagnose and treat.[11] Neonatal death rates are decreased when neonatal septicaemia is diagnosed early because it allows the clinician to start antibiotic therapy as soon as possible. Avoiding the needless treatment of a neonate who is not infected is another benefit of early detection of an infected baby. Neonatal sepsis cannot be definitively diagnosed in its early stages by a single, trustworthy test. For many years, the most often used parameter for identifying bacterial infections has been the C-reactive protein.[12,13]

One potential indicator of bacterial sepsis is procalcitonin (PCT). In this present study, among 195 neonates, 64.1% of the cases were labelled as probable sepsis and sepsis was indicated by procalcitonin levels (>0.5 ng/ml) in 37.4% and was confirmed on blood culture in 54.9% of the cases. Owing to early hospitalization, sample withdrawn prior to antibiotic administration, and appropriate aseptic methods throughout the collection process, nearly half newborns were diagnosed with sepsis confirmed on blood culture.

Our results are consistent with those of Chowdhury MSH et al., who enrolled 55 neonates, of whom 50.9% had clinical sepsis and 49.09% had confirmed sepsis.[10] The results are similarly comparable to those of the studies done by Naher BS et al. and Sucilathangam et al.[14,15] In addition to being time-consuming, the blood culture is difficult and yields little.[16] The leukocyte differential assay and the easily obtained complete blood count have a comparatively low specificity for sepsis diagnosis.[17] Although their subjective measurement is challenging, the related band count and a leftward shift of the myeloid immaturity measurements may increase the diagnostic result. Therefore, there is still a need for better newborn sepsis diagnostic signs.

In our study, serum procalcitonin demonstrated moderate sensitivity (51.4%) paired with high specificity (79.6%) and positive predictive value (75.3%) against confirmed sepsis on blood culture. Our findings are like those of Akter J et al., who found that PCT had a 48.6% sensitivity, 76.3% specificity, 66.7% PPV, and 60.4% NPV in detecting sepsis at a cut-off value >500 pg/ml.[9] Similar findings were shown in another investigation, where PCT's sensitivity and specificity in identifying sepsis were 46.4% and 75%, respectively, at a cut-off value > 500 pg/ml. Its PPV was 67.9%, while its NPV was 60.7%.[10]

Increased PCT levels were found in newborns with confirmed or clinically suspected conditions in earlier studies by Chiesa C et al[18] and Monneret G et al.[19]

Five out of six studies assessed the use of PCT in diagnosing NS in a systematic review conducted by Anugu NSR et al. PCT and the diagnosis of sepsis were positively correlated in all five investigations. When comparing PCT to CRP, all five trials found that PCT was more sensitive and accurate at identifying sepsis.[20] In a study by Habib A et al, 86 (50.3%) of the 171 clinically diagnosed cases of newborn sepsis were found to have neonatal sepsis (blood culture positive). PCT's diagnostic accuracy was 84.2%, its sensitivity was 97.7%, its specificity was 70.6%, its PPV was 77.1, and its NPV was 96.8%.[21]

Beaumont R et al examined 19 original studies that included 1920 infants with symptoms (721 of whom had sepsis). Six investigations with a PCT cut-off limit of 0.5 ng/mL reported 87% to 100% sensitivity and 17% to 89% specificity. High PCT cut-off limit between 0.9-2 ng/mL were assessed in nine investigations; these values were 41% to 89% specific and 67% to 98% sensitive.[22]

PCT is a great measure for early NS identification since it rises quickly with the onset of bacterial sepsis, unlike CRP. Differences in procalcitonin response to infection may be the cause of neonatal immunity being relatively compromised, systemic response to infection being blunted or absent, and neonates contracting bacteria (such as group B Streptococcus) that do not typically cause illness in older adults. Furthermore, the physiology of procalcitonin itself is distinct in neonates. In both healthy and sick neonates, the kinetics of procalcitonin levels fluctuate in the first 24 to 48 hours after delivery, peaking at 24 hours and then falling over the following 24 hours.[23] Lower weight on birth and gestational age are related with lower procalcitonin levels. Procalcitonin's diagnostic precision in the neonatal population has to be thoroughly and independently assessed.

CONCLUSION

Our study concludes that serum PCT value has moderate sensitivity and high specificity to diagnose sepsis in newborns. Our study contained small sample size, we suggest further large sized, multi-centered and follow up research studies for confirming PCT role in diagnosing neonatal septicemia.

CONFLICT OF INTEREST: All authors declared no conflict of interest exist.

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