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Original Research Article

Comparing Diagnostic Efficacy and Cost-Effectiveness of the Procalcitonin Test in Diagnosing Early Onset Neonatal Sepsis

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Abstract

Aim: To compare between the expenses and benefits of procalcitonin testing in the diagnosis of early onset neonatal sepsis.

Material and Methods: This research was conducted at the Department of Paediatrics at NMCH in Jamuhar, Sasaram, Bihar, India for 12 months.100 neonates who were born at or after 37 weeks of gestational age and were hospitalized to the Neonatal Intensive Care Unit (NICU) within 72 hours of delivery due to clinical symptoms or indications of sepsis, as well as those with risk factors for Early-Onset Neonatal Sepsis (EONS). All patients involved in the research had a comprehensive blood test, including a complete blood count with differential (CBC), CRP, blood culture, and procalcitonin, upon admission to the NICU. These tests were repeated after 8 hours, except for CRP which was repeated after 24 hours. Other cultures from other places, such as cerebrospinal fluid (CSF), were obtained, and appropriate chest x-rays and imaging studies were performed.

Results: The primary manifestation seen in this research was hypothermia, which occurred in 63% of cases. Hypoactivity and mottling were also common, reported in 54% of cases, followed by food intolerance in 43% of cases. 37 individuals had positive blood cultures, indicating that they had proved sepsis. Klebsiella was detected in 14 patients, E. coli in 10 patients, and group B streptococcus in 8 individuals. Three individuals were found to have Pseudomonas infection, while two patients tested positive for MRSA (methicillin resistant staphylococcus aureus). Out of the total number of patients, 42% had a non-reactive first CRP (CRP1). In the sepsis group, 42% had a non-reactive initial procalcitonin (PCT1), with 32% having a PCT1 value of less than 2.6, 20% having a value between 2.6 and 10, and 6% having a value higher than 10. The sensitivity of the test is 93.5%, meaning it correctly identifies 93.5% of the true positive cases. The specificity is 54%, indicating that it correctly identifies 54% of the true negative cases. The positive predictive value (PPV) is 66.3%, which means that 66.3% of the positive test results are true positives. The negative predictive PCT2: The sensitivity of the test is 96.8%, meaning it correctly identifies 96.8% of positive cases. The specificity is 88.7%, indicating that it correctly identifies 88.7% of negative cases. The positive predictive value (PPV) is 91.1%,

Conclusion: The cost of doing PCT testing twice is lower than the cost of a single day's hospitalization in the Neonatal Intensive Care Unit (NICU) in impoverished nations. Implementing such a policy might be beneficial in reducing the duration of hospitalization in the Neonatal Intensive Care Unit.

Key words: NICU, Procalcitonin, Early Onset Neonatal

Introduction

Early onset neonatal sepsis (EONS) remains a significant cause of morbidity and mortality among neonates globally. Prompt and accurate diagnosis is crucial for initiating appropriate treatment and improving outcomes. Traditionally, the diagnosis of EONS has relied on clinical signs and routine laboratory tests, which often lack specificity and sensitivity. This has led to the empirical use of broad-spectrum antibiotics, contributing to antibiotic resistance and increased healthcare costs. In this context, procalcitonin (PCT), a biomarker that rises in response to bacterial infection, has gained attention for its potential to improve the management of EONS by guiding antibiotic therapy decisions more accurately. [1,2] Procalcitonin levels increase significantly in bacterial infections but remain low in viral infections and inflammatory diseases, making it a promising tool for

distinguishing bacterial sepsis from other causes of neonatal distress. Several studies have highlighted the diagnostic accuracy of PCT in detecting neonatal sepsis, with some suggesting that PCT-guided therapy can reduce the duration of antibiotic treatment without compromising safety. [3,4] The cost-effectiveness of implementing PCT testing in the clinical management of EONS is a critical consideration for healthcare systems, particularly in resource-limited settings. By potentially reducing unnecessary antibiotic use, PCT testing may not only improve patient outcomes but also lower healthcare costs associated with prolonged hospital stays and the treatment of antibiotic-related complications. Recent economic evaluations have begun to assess the balance between the costs of PCT testing and the savings achieved through reduced antibiotic consumption and shorter hospitalizations. [5-9] A study by Schuetz et al. (2023) demonstrated that incorporating PCT testing in neonatal intensive care units (NICUs) could lead to significant cost savings, primarily by decreasing the duration of antibiotic therapy and reducing the incidence of antibiotic-associated adverse effects.[6] Another study by Simonsen et al. (2022) found that PCT-guided protocols were associated with a reduction in healthcare costs and improved antibiotic stewardship in neonates suspected of having EONS. [7] Despite these promising findings, the widespread adoption of PCT testing in the management of neonatal sepsis faces several challenges. These include the initial costs of implementing PCT assays, variability in test accuracy across different populations, and the need for clinical guidelines to standardize the use of PCT in neonatal care. Further research is required to validate these findings across diverse healthcare settings and to develop cost-effective strategies that integrate PCT testing into routine clinical practice. [8]

Material and Methods

This prospective observational study was carried out in the Department of Pediatrics, NMCH, Jamuhar, Sasaram, Bihar, India for 12 months. 100 Full-term neonates (>37 weeks gestational age) admitted to NICU with the clinical symptoms or signs of sepsis within 72 h of birth, and those with risk factors for EONS. The risk factors considered were: GBS infection during pregnancy, premature rupture of membrane, prolonged rupture >18 h before birth and Clinical syndrome of maternal intrauterine infection were included in this study. Patients < 37 weeks gestational age, patients with congenital anomaly or metabolic inborn error of metabolism, patients received antibiotics before admission to NICU and refusal of the parents to sign the consent were excluded from this study. For all patients included in the study, complete blood count with differential (CBC), CRP, blood culture, procalcitonin was done on admission to NICU, and was repeated after 8 hours from the initial one, while CRP was repeated after 24 hrs. Cultures from other sites (including CSF), chest x ray and imaging were done as appropriate.

Under complete aseptic conditions 3 ml of venous blood was collected, 1ml on ethylene diamine tetra acetic acid (EDTA) for complete blood count (CBC) and 2 ml was collected in plane tube and was left to clot then centrifuged to separate serum for estimation of serum CRP and detection of PCT. For serum PCT analysis Sera of the patients were analysed for PCT using commercially available Enzyme-linked immunosorbent assay (ELISA) kit. PCT production was calculated from a standard curve of the corresponding recombinant human PCT. Manual broth-based blood culture systems was used, namely non-selective agar media. Growth of any organism in samples taken from symptomatic newborns was taken significant.

Criteria for the Diagnosis of Neonatal Infection [10]

Temperature instability, Heart rate >180 beats/min or <100 beats/min, blood pressure 2 SD below normal for age, and capillary refill >3s. Respiratory problems: as apnea, dyspnea, retractions and cyanosis. Central nervous system affection: irritability, lethargy, abnormal Moro reflex, fontanel bulging, seizures, and hypotonia. Gastrointestinal system affection as feeding intolerance, abdominal dis- tension with repeated vomiting or frequent watery motions. leucocytosis (WBC>34000), leukopenia (WBC<5000), Thrombocytopenia<100000, CRP 2 SD above normal level, Procalcitonin 2 SD above normal value By the end of the first 48 h newborns were labelled proven infected if their blood culture showed growth of organism; and were continued on antibiotics. Another group were labelled infected but not proven and those include patients with positive CRP, leukopenia or leucocytosis, or if have clinical symptoms and signs of sepsis. The third group is the rest of the newborn suspected for EONS but without evidence, they were labelled suspected only, and their antibiotics were discontinued.

Statistical Analysis

P values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS 21.0.

Results

100 patients were included in the study, 68 females and 32 males. Their mean weight was 3.213 kg (range 2.2- 4.8 kg). Mean age of presentation was 14 hours (range 2-68) hours. 84 newborns (84%) presented within 28h of age, out of whom 54 newborns admitted at birth due to prolonged

rupture of membrane (18 h and more). Prolonged rupture of membrane was the main risk factor, followed by maternal infections and fever (29 patients), fetal tachycardia (15 patients), and smelly liquor (7 patients). Table 1 shows the clinical features of the newborns on admission to NICU About 90 (90 %) patients presented with more than one symptom and signs of sepsis For CBC results, mean WBC count was 19.8± 9.1, the mean neutrophils count was 15.55± 10.57) and the mean platelet count was 171.21±69.21. This study includes neonates with early onset sepsis. In the present study the most frequent presenting sign was hypothermia (63%), hypoactivity and mottling (54%), followed by feeding intolerance (43%).

Table 1: clinical symptoms and signs of the patients

Clinical symptoms and signs	Number of patients	Percentage
Tachypnea	37	37
Tachypnea with intercostal retractions	20	20
Sudden desaturation	14	14
Tachycardia	8	8
Bradycardia	17	17
Feeding intolerance,	43	43
vomiting	12	12
Hypothermia	63	63
Hypo activity, mottling	54	54

Blood cultures were positive in 37 patients, who compromised the group of proven sepsis. Klebsiela was present in 14 patient, E coli in 10 patients, while group B streptococcus in 8 patients. Pseudomonas infection present in 3 patients, while MRSA (methicillin resistant staphylococcus aureus) was detected in 2 patients. The initial CRP (CRP1) , was non-reactive in 42 patients (42%), The initial procalcitonin in the sepsis group (PCT1), was non-reactive 42 patients (42%) , <2.6 in 32 patients (32%), 2.6-10 in 20 patients (20%), and more than that in 6 patients (6%). Table (2) shows CRP1/PCT1 results in the group with proven sepsis and those infected but not proven in Table (3). CRP2/PCT2 for the two categories are shown in Table 4 and 5. Table 6 shows work out of the predictive values of CRP2 and PCT2.

Table 2: Results of CRP1 and PCT1 in newborns with proven sepsis

	Positive	Negative	Total	
CRP1	26	11	37	
PCT1	28	9	37	
Total	54	20	74	0.31
	0.31			

Table 3: Results of CRP1 and PCT1 in newborns with not-proven sepsis

	Positive	Negative	Total
CRP1	8	34	42
PCT1	5	37	42
Total	13	71	84
p-value	0.063		

Table 4: Results of CRP2 and PCT2 in newborns with not-proven sepsis

	Positive	Negative	Total
CRP2	32	5	37
PCT2	33	4	37
Total	65	9	74
p-value	0.061		

Table 5: Results of CRP2 and PCT2 in newborns with not-proven sepsis.

	Positive	Negative	Total
CRP2	21	21	42
PCT2	6	36	42
Total	27	57	84
p-value			0.004

Table 6: The predictive value for CRP2 and PCT2 in diagnosis of EONI.

	Positive	Treated group	Not treated group	Total
CRP2	Positive	56	24	80
	Negative	3	17	20
PCT2	Positive	52	5	57
	Negative	5	38	43

CRP2: Sensitivity= 93.5%, Specificity=54%, PPV= 66.3%, NPV= 87.5%. PCT2: Sensitivity=96.8%, Specificity=88.7%, PPV=91.1%, NPV=99%.

Managing infants in the three groups (proven, not-proven, and suspected infection) resulted in 412 inpatient days. The 37 patients in the group of proven infection (37%) were admitted for 10-14 days but 5 of them needed more than 2 weeks admission. 5 patients of this group died due to infection with GBS which caused bacteraemia, followed by toxic myocarditis and heart failure, that didn't respond to the antibiotic course. The second group (not-proven infection) of 42 patients (42%) were discharged within 4 days of admission, and they did well on the follow up except for 10 patients who didn't show up. The third group 21 patients (21%)with suspected infection, treated with antibiotics for at least 10 days, and all of them did well on the follow up.

Discussion

This study includes neonates with early onset sepsis. In the present study the most frequent presenting sign was hypothermia (63%), hypoactivity and mottling (54%), followed by feeding intolerance (43%). Mamta et al, [11] reported refusal to feed (77%), respiratory distress (44%), and hypothermia (47.5%), while Khatua et al., [12] re- ported refusal to feed (92%), lethargy (74%), hypothermia (72%) and respiratory distress (24%) as common clinical presentation. In agreement with the study done by Muhammed et al, the most frequent recognized risk factor in the present study, was premature rupture of membrane (PROM). [13]

A study from Bangladesh showed that approximately one-third of all septicaemia in neonates was attributable to premature rupture of membranes. [14] While a study from Thailand reported 27.9% of cases with EONI is due to PROM. [15] For such patients rapid diagnosis of early onset sepsis is needed, to avoid unnecessary stay in NICU, which in turn increase the economic and social burden in already poor settings. In agreement with the study done by Hornik [16] and Altunhan [17], CBC findings in this study was not informative, and didn't help in the diagnosis of sepsis. Also the British evidence update advisory group didn't recommend the use of CBC in the diagnosis of neonatal sepsis. [18] Camacho A, [19] stated that complete blood count is difficult to interpret in the neonatal period because it varies significantly with day of life and gestational age, and they are poor indicator of sepsis.

In this study the predominate organism isolated from patients with proven sepsis was Klebsiela 14%, followed by Ecoli 10%, this is in congruous with Zaidi et al [20] and Downie L, [21] who stated that Klebsiela is the most predominate organism in developing countries in both Hospital and community- acquired infection. In contrast to other studies which stated that GBS is the most common pathogens of early onset sepsis in developed countries, but its burden in developing countries is less clear due to lack of studies using optimal diagnostic tools. [22] GBS present in 8% of the patients of this study, done in a developing country. This can be explained, as the most frequent risk factor detected in this study was premature rupture of membrane and maternal infection which in turn increase the possibility of neonatal infection with GBS.

MRSA was detected in 2% of the patients in this study, nasal swabs from the NICU staff and swabs from the incubators were taken to detect the source of infection. Two nurses from the staff were MRSA positive; they were isolated and received treatment for 10 days. Zaidi et al [23] reported most pathogens isolated in the hospital setting before 72HR of life are similar to those isolated afterwards; it is likely that highly unclean delivery practices lead to infections with nosocomial agents very early in life. Table 2 and 3 compare the results of CRP1 and PCT1 in the category of proven sepsis and not-proven sepsis. In both categories there was no significant difference between CRP1 and PCT1 in the ability to support the diagnosis of neonatal infection or refute it. In the group with suspected sepsis there was no significant difference between PCT1 and CRP1 in distinguishing patients with neonatal sepsis. Blommendahl J [24] stated that PCT

was not a better marker than CRP levels because PCT is affected by perinatal factors within 48h of birth making its usefulness in diagnosing of early onset sepsis very limited. Other than infection, PCT levels increase in premature infants, hypoxia, RDS, and hemodynamic instability, decreasing its specificity in early onset sepsis. [25] In this study CRP was repeated over 24 hours, while PCT was repeated after 8 hours to increase their reliability, the same was done in the study of Blommendahl et al, [24] and the study done by Hengest 2003. [26] Analysis of table 4 revealed that both CRP2 and PCT2 tests were able to differentiate more between infected and not infected newborns but there was no-significant difference between the two tests (P value 0.061). For the group of newborns with not-proven sepsis as shown in table 5, there was significant difference between both tests (P value 0.004), PCT2 can distinguish more accurately between cases with possible sepsis and cases with no sepsis. Compares predictive values for CRP2 and PCT2 Sensitivity= 93.5%, Specificity=54%, PPV= 66.3%, NPV= 87.5%. PCT2: Sensitivity=96.8%, Specificity =88.7%, PPV=91.1%, NPV=99%. Procalcitonin evaluation done by Chaurasiya et al, [27] demonstrated sensitivity of 96.25%, specificity of 85%, PPV of 96.25% and NPV of 85%. Claudio Chiesa et al [28]studied the reliability of PCT concentration in 28 infants with severe early onset sepsis. They observed that the sensitivity 92.6%, specificity 97.5%, PPV 94.3%, NPV 96.5% respectively.

Conclusion

The cost of doing PCT testing twice is lower than the cost of a single day's hospitalization in the Neonatal Intensive Care Unit (NICU) in impoverished nations. Implementing such a policy might be beneficial in reducing the duration of hospitalization in the Neonatal Intensive Care Unit.

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