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Cost-Effectiveness of Procalcitonin test in Cases with Early Onset Neonatal Sepsis in Egyptian Governmental Hospitals

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Abstract

Objectives: To compare between the expenses and benefits of procalcitonin testing in the diagnosis of early onset neonatal sepsis in Egyptian Governmental Hospitals.

Methods: Admitted newborns were investigated for neonatal sepsis including CBC, blood culture, CRP, and PCT. They were given Ampicillin and Gentamicin which were changed as per blood C/S results or according to clinical progress. CRP and PCT were done initially. PCT was repeated 8h and CRP 24h later. Three categories were identified: proven sepsis with positive blood culture, not-proven sepsis with negative blood culture, and suspected sepsis with no clinical or laboratory evidence of infection .PCT levels were compared to CRP levels in all categories.

Results: eighty-nine newborns with neonatal sepsis were included, mean weight was± 3.150 kg. Mean age at presentation was ±14 hours. clinical features of the newborns on admission to NICU were presented in table (1).Twenty- nine infants were proven neonatal sepsis. Isolated organisms were: 9 Klebsiela, 7 Ecoli, 6 Group B streptococci, 4 Pseudomonas, and 3 MRSA. Thirty- six with not-proven sepsis, while twenty-four had suspected sepsis. 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. Comparing the predictive values of PCT2 and CRP2, PCT2 has higher sensitivity and specificity than CRP2.Repeat PCT had better ability to distinguish infected from non-infected patients.

Discussion: both CRP and PCT were good to guide management of neonatal sepsis, but repeat PCT after 8 h after initiation of antibiotics treatment might be enough to detect precisely cases with early onset sepsis, with no need to wait for results of blood culture, especially in countries with limited resources.

Conclusion: The expense of testing PCT twice is less than the expenses of one-day admission in NICU in developing countries. Application of such protocol could be of use in limiting period of stay in NICU.

Keywords: Neonatal sepsis, PCT- Egyptian Hospitals

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Introduction

Neonatal mortality account for 40 % of all deaths of children under age of 5 years. The time of birth and first days of life are the riskiest period in the human life span[17]. Early onset neonatal sepsis (EONS) refers to infection arising within first 72 h after birth[12]. Sepsis shares a similar clinical presentation to other common conditions in the neonatal period. The evaluation of neonatal infection by laboratory test is important because the infection may present a very serious threat to the baby. There is an urgent need to know whether the baby has sepsis to institute treatment as quickly as possible and to avoid unnecessary stay in NICU[5].

Automated blood culture systems have long been considered the gold standard for microbiological diagnosis. However, despite improvement in growth media and instrumentation, results of blood culture can be delayed by up to 48 hours[5-13-24]. The condition of a neonate with true sepsis can deteriorate quickly; thus, the most common approach is to initiate empiric broad-spectrum antibiotic therapy in all young infants with suspected bacterial infection[27]. A negative blood culture after 48 hours may allow cessation of antibiotic therapy in a well infant.[2]

Although neutrophil, total white blood cell (WBC), absolute neutrophil count (ANC), and platelet counts are ordered to screen for suspected

sepsis, these values are ineligible as infection markers due to insufficient sensitivity and specificity[25]. Thus, most hospitals commonly use C-reactive protein (CRP) levels as markers.

Procalcitonin (PCT), a precursor of calcitonin, is a 116 amino acid protein secreted by the C cells of thyroid gland in normal situation but its levels may increase during septicemia, meningitis, and pneumonia and urinary tract infection.[20, 26]. Recently, the effectiveness of procalcitonin (PCT) as an early diagnostic tool for neonatal sepsis has been reported. Research studies reported that PCT is more effective than CRP at follow up, as PCT levels rise earlier and return to normal levels more rapidly than CRP levels .[10,25, 27].

The management of neonatal sepsis in developing countries is aggravated by increased levels of antibiotic resistance, shortage of medical personnel and high numbers of home-births. Multiple studies, some of them still ongoing, have addressed these difficulties. Additionally, some developing countries have started to implement tertiary care units and are now facing the challenges of developed countries as well.[1]

Procalcitonin (PCT) is not one of the routine investigations in Egyptian Governmental Hospitals due to its high cost (single test cost about 40 US dollars), in contrast to the other sepsis markers as CBC, CRP, Blood culture which are routinely done for all patients admitted to the NICU. In this study we tried to compare the expenses of procalcitonin test with its benefits in early diagnosing and follow up of cases with early onset neonatal sepsis (EONS), as blood cultures take about 48-72 hours to give its primary results. This will reduce the stay in NICU, thus lessen the expenses of unnecessary stay in such units, in countries with poor resource.

Aim of the study

To compare between the benefits of using procalcitonin for diagnosing neonatal sepsis in Egyptian Governmental Hospitals with limited resources, with the cost of procalcitonin test if done for all patients with suspected early onset infection in Neonatal Intensive Care Units(NICU).

Methods and Material

This is a prospective, observational study, carried out in Abo EL Rish Teaching Hospital, Cairo, Egypt. The hospital has a capacity of 20 incubators, with all facilities for intensive care and good laboratory back up. All patients admitted for 1 year in the unit, which was a series of 89 cases, were included in the study. The study started on June 2016 .

Sample size: since there were no previous reports of incidence it was decided to take a convenience sample of all casas admitted for one year which was a series of 89 case.

Inclusion criteria: 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.

Exclusion criteria: 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.

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 , 1 ml 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. CBC was done on Sysmex KX-21N and blood films were prepared as described by (Barbra and Imelda 2005) for morphological examination. C reactive protein was assayed using Cobas Integra systems. (Cobas Integra C-Reactive Protein Latex;Roche Diagnostics). For serum PCT analysis Sera of the patients were analyzed for PCT using commercially available Enzyme-linked immuno sorbent assay (ELISA) kit, following the manufacturer's instructions (MBL and R&D systems). 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[11]

Clinical variables: 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.Gastro-intestinal system affection as feeding intolerance, abdominal distension with repeated vomiting or frequent watery motions.

Laboratory variables: leukocytosis (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 labeled proven infected if their blood culture showed growth of organism; and were continued on antibiotics. Another group were labeled infected but not proven and those include patients with positive CRP, leukopenia or leukocytosis, 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 labeled suspected only, and their antibiotics were discontinued.

Newborns were started on ampicillin and gentamicin as first line antibiotics awaiting blood culture results. For patients with cultures negative at 24-48 hours, antibiotics were discontinued if the baby is asymptomatic and labs are normal.

Statistical analysis

The EPI info programme was used for data entry and analysis. Chi square test was used for calculation of significance. P values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006).

Results

89 patients were included in the study, 50 females and 39 males. Their mean weight was 3.150 kg (range 2.2- 4.6 kg). Mean age of presentation was 14 hours (range 2-71) hours. 70 newborns (78.6%) presented within 28 h of age, out of whom 44 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 (24 patients), fetal tachycardia (16 patients), and smelly liquor (5 patients)

Table 1 shows the clinical features of the newborns on admission to NICU About 78 (87.6 %) patients presented with more than one symptoms and signs of sepsis For CBC results, mean WBC count was± 18.7 (SD 9.821), the mean neutrophils count was ±14.43 (SD 11.46) and the mean platelet count was ±±167.11 (SD 69.86).

Clinical symptoms and signs	Number of patients	Percentage
Tachypnea	34	38.22 %
Tachypnea with intercostal retractions	18	20.22%
Sudden desaturation	12	13.48%
Tachycardia	7	7.86%
Bradycardia	15	16.85
Feeding intolerance,	36	40.44%
vomiting	9	10.11%
Hypothermia	54	60.67%
Hypo activity, mottling	46	51.68%

Table 1: shows the clinical symptoms and signs of the patients included in the study

Blood cultures were positive in 29 patients, who compromised the group of proven sepsis. Klebsiela was present in 9 patient, E coli in 7 patients, while group B streptococcus in 6 patients. Pseudomonas infection present in 4 patients, while MRSA (methicillin resistant staphylococcus aureus) was detected in 3 patients.

The initial CRP (CRP1) , was non-reactive in 39 patients (39.79%), <10 in 25 patients (25.51%), 10-20 in 23 patients (23.46%), and more than that in 11 patients (11.22%).

The initial procalcitonin in the sepsis group (PCT1), was non-reactive 39 patients (43.83%) , <2.6 in 26 patients (29.21%), 2.6-10 in 18 patients (20.22%), and more than that in 6 patients (6.74%).

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.

	Positive	Negative	Total
CRP1	20	9	29
PCT1	22	7	29
Total	42	16	58 Pvalue 0.3924

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

	Positive	Negative	Total
CRP1	6	30	36
PCT1	4	32	36
Total	10	32	72 Pvalue 0.067

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

	Positive	Negative	Total
CRP2	26	3	29
PCT2	27	2	29
Total	53	5	58 Pvalue 0.070

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

	Positive	Negative	Total
CRP2	18	18	36
PCT2	6	30	36
Total	24	48	72 Pvalue 0.004

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

	Positive	Treated group	Not treated group	Total
CRP2	Positive Negative	45 3	21 20	66 23
PCT2	Positive Negative	47 5	2 35	49 40

Table 6: The predictive value for CRP2 and PCT2 in diagnosis of EONI.
CRP2: Sensitivity= 91.5%, Specificity=52%, PPV= 64.3%, NPV= 85.5%.
PCT2: Sensitivity=94.8%, Specificity=86.7%, PPV=89.1%, NPV=97%.

Managing infants in the three groups (proven, not-proven, and suspected infection) resulted in 402 inpatient days. The 29 patients in the group of proven infection (32.58%) were admitted for 10-14 days but 4 of them needed more than 2 weeks admission. Three patients of this group died due to infection with GBS which caused bacteremia, followed by toxic myocarditis and heart failure, that didn't respond to the antibiotic course. The second group (not-proven infection) of 36 patients (40.44%) were discharged within 4 days of admission, and they did well on the follow up except for 6 patients who didn't show up. The third group 24 patients (26.96%)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 (60.67%), hypoactivity and mottling (51.65%), followed by feeding intolerance (40.44%). Mamta et al, (19) reported refusal to feed (77%), respiratory distress (44%), and hypothermia (47.5%), while Khatua et al., (15) reported 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). [22]

A study from Bangladesh showed that approximately one-third of all septicemia 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.[24]

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[13] and Altunhan (2), 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.[21]

Camacho A, (6) stated that complete blood count is difficult to interpret in the aneonatal 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 31%, followed by Ecoli 24%, this is in congruous with Zaidi et al[29], and Downie L,(9), 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.[23] GBS present in 21% 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 3.37% 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[28],reported most pathogens isolated in the hospital setting before 72h of life are similar to those isolated afterwards; it is likely that highly unclean delivery practices lead to infections with noso-comial 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 (4) 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.[16]

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,(4) and the study done by Hengest 2003.[12] 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 0.070). 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.

Table 6 compares predictive values for CRP2 and PCT2 with better sensitivity, stronger specificity and high predictive values for PCT2. PCT2: Sensitivity=94.8%, Specificity=86.7%, PPV=89.1%, NPV=97%.

Procalcitonin evaluation done by Chaurasiya et al,(7) demonstrated sensitivity of 96.25%, specificity of 85%, PPV of 96.25% and NPV of 85%. Claudio Chiesa et al (8) 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.

It is clear from the previous data, that PCT didn't give additional information superior to that of CRP in diagnosing cases with suspected sepsis, in cases where blood culture results were not yet available. However, repeated PCT was more accurate than CRP in differentiating cases with sepsis. This means that the protocol of repeat test of PCT after 8 hours from the initial assessment could be of great benefit in diagnosing cases with early onset sepsis, thus reducing unnecessary stay in NICU, and over-use of antibiotics.

WHO developed the ASSURED criteria for an ideal point of care test in resource-limited settings, taking its accuracy and reliability as the main features.[18] PCT fulfills these criteria and the cost of assessment of PCT level twice for each patient is less than the cost of one day admission in NICU.

Making use of accuracy of PCT2 in detecting cases with neonatal sepsis, could have saved about 30 % of total admission days. Comparing this to the cost of the test, the benefit of assessing PCT is clear.

Limitation of the study: using the protocol of using PCT2 in all NICU, needs more studies on a wider scale to be done, using more number of patients and over more extended period of time.

Conclusion

This prospective study compared between expenses of procalcitonin test in developing countries, with limited resources, and the benefit from using such test in diagnosing cases with early onset sepsis. The study revealed, assessing PCT done few hours from the primary one (PCT2) , could be of great help in diagnosing patient with early onset sepsis , and is more accurate than CRP alone. Use of PCT2 could reduce the length of stay in NICU, thus reduce the expenses of unnecessary stay in such units.

Conflict of interest:

The authors have no conflicts of interest relevant to this article.

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