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Evaluation of Biomarkers in the diagnosis of Neonatal Sepsis

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ABSTRACT

INTRODUCTION:- *Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteremia in the first month of life. It encompasses various systemic infections of the newborn such as septicemia, meningitis, pneumonia, arthritis, osteomyelitis and urinary tract infections. Superficial infections like conjunctivitis and oral thrush are not usually included under neonatal sepsis. Neonatal sepsis is a worldwide problem that presents a management challenge to care groups for neonates and infants.*

OBJECTIVE:-*To compare the role of Procalcitonin, CRP, TLC, ANC, Band forms count, I/T ratio, Toxic Granules, Thrombocytopenia and microESR in diagnosis of neonatal sepsis.*

DESIGN:- *Prospective study*

SETTING:- *Neonates meeting the Inclusion Criteria of our study were admitted to NICUs of Mahadevappa Rampure Medical College, Kalaburagi, from December 2013- May2015*

PARTICIPANTS/PATIENTS:- *85 neonates were included in the study based on the following inclusion criteria. 1) Neonates born to mothers with at least one of the*

following features:- *PROM > 18 hours, >3 vaginal examinations, maternal fever (> 38° C) since one week before delivery, foul smelling liquor, meconium stained liquor, untreated or partially treated urinary tract infection and prolonged and difficult delivery with instrumentation 2) Neonates admitted with signs suggestive of sepsis as per IMCI guidelines or those who developed signs of sepsis during their stay in the hospital.*

RESULTS:- *Of the 85 neonates studied, 32 were diagnosed as proven sepsis, 34 as probable sepsis and 19 as no sepsis. The most common organism isolated on blood culture was Staphylococcus aureus. TLC, ANC, Band Count, I:T, microESR, Thrombocytopenia, Toxic granules showed low sensitivity (6%, 6.2%, 34.3%, 28.1%, 28.1%, 56.2% and 28.1%) and moderate to high specificity (96.2%, 96.2%, 88.6%, 64.1%, 98.1%, 84.9% and 62.2%), whereas CRP and PCT had high sensitivity (90.6%, 90.6%), moderate specificity (69.8%, 83%) and moderate accuracy (77.6%, 85.8%).*

CONCLUSION:- *Procalcitonin (>2ng/ml) with higher accuracy (85.8%) appears to be a better test for diagnosis of neonatal sepsis.*

KEYWORDS : Biomarkers, CRP, Neonatal sepsis, PCT

INTRODUCTION

Neonatal sepsis is a worldwide problem that presents a management challenge to care groups for neonates and infants. It has been explained that neonates are at the greatest risk for bacterial sepsis with a prevalence of 1 to 10 per 1000 live births worldwide. Existing published data have suggested that sepsis causes about 26% of all neonatal deaths [1, 2] Sepsis related mortality is largely preventable with prevention of sepsis itself, timely recognition, rational antimicrobial therapy and aggressive supportive care.

In a report of the National Neonatal Perinatal Database, Klebsiella pneumoniae was the most frequently isolated pathogen (32.5%), followed by Staphylococcus aureus (13.6%). Among extramural neonates (referred from community/other hospitals), Klebsiella pneumoniae was again the commonest organism (27%), followed by Staphylococcus aureus (15%) and Pseudomonas (13%). [3]

Neonatal sepsis according to age of onset:1] Early onset sepsis (EOS):It presents from birth to 7th day of life [usually <72 hrs] in severe cases, the neonate may be symptomatic at birth. The source of infection is genital tract of mother. Respiratory distress and pneumonia are usual presentations. 2] Late onset sepsis (LOS): It usually presents after 7th days of life. Source of infection is either nosocomial or community acquired. They usually present with septicemia, pneumonia or meningitis. [4,5, 6]

Neonates with bacterial sepsis may have either nonspecific signs and symptoms or focal signs of infection, including temperature instability, hypotension, poor perfusion with pallor and mottled skin, metabolic acidosis, tachycardia or bradycardia, apnea, respiratory distress, grunting, cyanosis, irritability, lethargy, seizures, feeding intolerance, abdominal distention, jaundice, petechiae, purpura, and bleeding. The initial manifestation may involve only limited symptomatology. Later complications of sepsis include respiratory failure, pulmonary hypertension, cardiac failure, shock, renal failure, liver dysfunction, cerebral edema or thrombosis, adrenal hemorrhage and/or insufficiency, bone marrow dysfunction and DIC. [6] Laboratory evaluation of a neonate with symptoms includes total counts with differential counts, Absolute neutrophil counts (ANC),Absolute band count, immature to total neutrophil ratio [I: Tratio], Toxic granules and blood culture. All these apart from blood culture do not have high sensitivity especially in early disease course and it takes upto 72 hrs for blood culture to isolate organisms. Owing to this delay in definitive diagnosis some other tests have been evaluated like C-reactive proteins and Procalcitonin.

CRP is an acute phase reactant produced by liver in response to inflammation. Alone it is of little value in early onset sepsis but has better PPV and specificity in Late Onset Neonatal Sepsis (LONS). PCT is another acute phase reactant produced by macrophages in response to inflammation.

Levels of PCT are affected by postnatal age necessitating its careful interpretation in Early Onset Neonatal Sepsis (EONS). An elevated level of PCT has been shown to have a moderate sensitivity and specificity for Early as well as LONS. Due to heterogeneous methods, wide range of subjects and varied definition of sepsis the sensitivity of PCT varies in different studies. [7] IL-6 has also been reported as early marker for neonatal sepsis. [8, 9] Raised IL-6 had a high sensitivity and negative predictive value of 89-91 % for late onset sepsis in one study. [9] Its rise precedes CRP hence it is very early marker of sepsis however its estimation is not feasible for clinical use at present.

Clinical signs of sepsis are non-specific and there are no reliable early laboratory indicators. As early and efficient antibiotic therapy is needed to improve the prognosis of sepsis there is a need for sensitive and specific indicators for sepsis at the earliest stage of the disease. This study was undertaken to find out the usefulness of various biomarkers used to assess neonatal sepsis.

METHODS

The present study was a Prospective clinical study conducted at the NICUs of Basaveshwar Teaching&General Hospital and Sangameshwar Teaching&General Hospital attached to Mahadevappa Rampure Medical College, Kalaburagi, Karnataka, from December 2013- May 2015. All neonates born to mothers with at least one of the following risk factors are included, i.e., Premature rupture of membranes (PROM)>18 hours, More than 3 vaginal examinations after rupture of membranes, History of maternal fever (>38° C) since one week before delivery, Foul– smelling liquor, Meconium stained liquor, Untreated or partially treated urinary tract infection, Prolonged and difficult delivery with instrumentation. Neonates admitted with signs suggestive of sepsis or those who developed signs of sepsis during their stay in the hospital were also included. Those excluded from the study were New born babies with gestational age less than 28 weeks, Neonates with birth weight less than 1000gm, All children more than 28 days of life, Still born and dead fetuses, Infants who were on antibiotics or who developed signs of sepsis within 72 hrs of discontinuation of antibiotics, Laboratory finding suggestive of inborn error of metabolism and congenital anomalies and Neonates with lethal congenital anomalies. Written, valid and informed consent was taken from parents or care takers of the subjects included in the study and the disease process and importance of treatment was explained to them. Maternal history and risk factors noted and Investigations recorded in case of presence of maternal risk factors. All the neonates in the study were investigated with Total leukocyte count, Absolute neutrophil count, Band forms count, Immature / Total neutrophil (I/T) ratio and Toxic Granules, Micro ESR, Blood culture, CRP and Procalcitonin. Chest X-ray was done in neonates with respiratory distress to rule out pneumonia. Complete blood count was done using Automated Analyzer. Total count, differential count, platelet count were reconfirmed in peripheral smear study. Band cells count to calculate immature to total neutrophil count, were also done in peripheral smear study. C-reactive protein was done using Quantia CRP UV-Turbidimetric immunoassay. QUANTIA CRP UV is a turbidimetric immunoassay for determination of C-reactive protein in human serum and is based on the principle of agglutination reaction. The test specimen is mixed with activation buffer (R1), Quantia CRP UV-reagent (R2) is then allowed to react. Presence of CRP in the test specimen results in formation of an insoluble complex producing a turbidity, which is measured at 340 nm wave length. The increase in turbidity corresponds to concentration of CRP in the test specimen. Procalcitonin levels were done in the serum using B·R·A·H·M·S PCT LIA is an immunoluminometric assay (ILMA) B.R.A.H.A.M.S kit which determines PCT. Levels of <0.5ng/ml: No sepsis. Measurable, but clinically insignificant, >0.5-<2ng/ml: Probable sepsis significant, but moderate SIRS. Infection is possible, and >2 ng/ml: Sepsis, Severe systemic inflammatory response most likely due to infection, unless other causes are known.

The BRAHMS PCT LIA assay uses two monoclonal antibodies that are directed against the Cterminal and mid-regional catacalcin sequences. The anti-catacalcin antibody is immobilized on the surface of the coated tube, and the anti-calcitonin antibody is labelled using a luminescent acridine derivative. The assay remains unaffected by calcitonin and catacalcin levels, even at highconcentrations. 20-µl serum or plasma samples are used for the PCT test. The samples are incubated at room temperature for 1 hour. The samples are placed in a luminometer and hydrogen peroxide and sodium hydroxide solutions are automatically injected. These substances reaction with the acridine derivative bound to the anti-calcitonin antibody, which emits light as it transforms into acridone. The emitted light intensity is directly proportional to the PCT concentration. As per clinical findings and blood results neonates were classified into 3 groups:1) *Definite sepsis*: Neonate with signs and symptoms (as described in IMCI) suggestive of sepsis with a positive blood culture.2) *Probable sepsis*: Will be based on any one of the following:-i) Two or more signs suggestive of sepsis (as described in IMCI) with at least one abnormal laboratory parameter (as described in Table I), ii) One or more signs (as described in IMCI) suggestive of sepsis with two or more abnormal laboratory parameter (as described in Table I). 3) *No Sepsis*: cases not coming under Definite and Probable sepsis. The data obtained from the study was analyzed with the statistical software namely SPSS 15.0, Stata 8.0, Med Calc9.0.1 and Systat 11.0.

RESULTS

The present study was conducted from December 2013 to May 2015.A total of 85 neonates were studied, out of which 34(40%) were diagnosed as probable sepsis, 32(37.6%) as proven sepsis and 19(22.4%) as no sepsis. The most common organism isolated in blood culture was Staphylococcus aureus (50%). 50.5% were males and 49.4% were females. Majority of neonates were term (59%) followed by preterm (26%) & post terms (15%). Majority (57%) of neonates were between 1.5 and 2.5 kgs. Majority of the proven sepsis neonates were females (62.5%) and that of probable sepsis were males (64.7%). Majority of newborn in all the 3 categories (proven, probable and no sepsis) were term neonates 70.6% of neonates were diagnosed with LONS and 29.4 % with EONS. Majority of neonates with EONS (68%) and LONS (83.3%) were delivered outside our hospitals. Majority of the neonates in the EONS category were diagnosed as Probable sepsis (44%) and those in the LONS category were either Proven or Probable sepsis (38.3% each). PROM >18 hours was present in 36% of neonates diagnosed with EONS. Refusal of feeds was the most common complaint and was seen in 62.4% of the cases, followed by reduced movements and lethargy seen in 62.1% of the cases. Total Leucocyte count had low sensitivity (18.7%), a moderate specificity (79.2%), moderate PPV, NPV (35.2%, 61.7% respectively) and Accuracy of 56.4%. Absolute Neutrophil Count had low sensitivity (6.2%), a high specificity (96.2%), moderate PPV, NPV (50%, 62.9% respectively) and Accuracy of 62.3%. Absolute Band Count had low sensitivity (34.3%), a high specificity (88.6%), moderate PPV, NPV (64.7%, 30.8% respectively) and Accuracy of 68.2%. Toxic granules had low sensitivity (28.1%), a moderate specificity (62.2%), low PPV, NPV (31%, 58.9% respectively) and Accuracy of 63.5%. Micro ESR had low sensitivity (28.1%), a high specificity (98.1%), high PPV (90%), moderate NPV (69.3%) and a moderate Accuracy of 71.7%. Thrombocytopenia had low sensitivity (56.25%), a high specificity (84.9%), moderate PPV, NPV (69.23%, 76.27% respectively) and Accuracy of 74.1%. I: T Ratio had low sensitivity (28.1%), a moderate specificity (64.1%), low PPV and NPV (32%, 59.6% respectively) and Accuracy of 50.5%. CRP at a cut-off value of 10mg/dl had high sensitivity (90.63%), a moderate specificity (69.8%), moderate PPV (64.44%), high NPV (92.5%) and Accuracy of 77.6%. PCT at a cut-off value of 2ng/ml had a high sensitivity and NPV (90.6% and 93.6% (respectively), a moderate specificity and PPV (83% and 76.3% respectively) and Accuracy of 82.8%. The mean value of CRP in proven, probable and no sepsis group were 44.7 mg/dl, 15.85 mg/dl and 5.81 mg/dl respectively. Mean values for PCT in proven, probable and no sepsis group were 32.6ng/ml, 2.07ng/ml and 0.61ng/ml respectively. The P value was < 0.0001 for PCT and CRP which is considered extremely significant.

DISCUSSION

The diagnosis of sepsis has always been difficult. It has always been shown that the problem if tackled early, can decrease the morbidity and mortality significantly. This prospective study has confirmed some well-known observations. In this study, majority of neonates in the proven and probable sepsis group were term, probably due to the fact that most of the babies in NICU were referred cases and do not necessarily represent an ideal population base. Anderson-Berry et al (2008) in their study showed that sepsis is more common in preterm neonates. [11] The contradictory inference of our study may be probably due to good ANC care, avoidance of pre-term births by health education, early,recognition of high risk pregnancies and suitable treatment.

According to the updated Merck Manual (2005), low birth weight neonates were at a higher risk for sepsis and meningitis. [12] In our study, neonates with birth weight between 1.5-2.5 kg were most affected with sepsis (47% in probable sepsis group and 62.5% in proven sepsis group). Anderson et al also have shown increased risk as the birth weight decreases. [13] Yancey et al (2003) reported that neonatal sepsis was associated with PROM in (56.23%) of cases. [14] In our study, 36% of the neonates with early onset neonatal sepsis had mothers with PROM. Tachypnea is the most common presentation of early onset neonatal sepsis. [15] Majority of the neonates in our study presented with refusal of feeds (62.4%) followed by reduced movements and lethargy (62.1%), Tachypnea (48.1%), Chest indrawing (41.2%), Nasal flaring, fever, prolonged capillary refill time (38.8%) and seizures (20%). Procalcitonin and positive CRP were found to be the most sensitive tests (sensitivity 90.6% for both) with specificity of 83% and 69.8% respectively with 'p' value of <0.001. Other studies with similar findings have been shown in Table 6. All studies in neonates report a higher sensitivity for procalcitonin than for CRP [16, 17, 18, 19] and a lower specificity for procalcitonin than for CRP. [17, 20] There are many pitfalls but still procalcitonin performs better than CRP in diagnosing neonatal bacterial infection. First, the infants with the respiratory distress syndrome, hemodynamic failure, perinatal asphyxia, intracranial hemorrhage and pneumothorax or after resuscitation have serum procalcitonin concentrations that do not differ from those of septic neonates upto 48 hrs after onset of clinical signs of distress or infection.[20, 21, 22]] Second, a physiological increase of procalcitonin has been reported upto 48 hrs postpartum.[16, 21, 23, 24] Third, prepartum and intrapartum administration of antibiotics may affect procalcitonin concentrations in umbilical cord and postnatal administration of antibiotics will decrease procalcitonin concentrations more rapidly than CRP concentrations.[25, 26]

CONCLUSION

Currently available investigations diagnosing neonatal sepsis require a long time in obtaining results hence there is a dire need for early marker of neonatal sepsis. Procalcitonin can be detected 6-12 hours after the infectious insult and its levels also correlate well with the degree of insult. It can also thus be used to prognosticate the neonate. It has a high sensitivity which is related to its rapid response time which is much faster than that of CRP and should thus help to gain time for diagnosis. The amount of blood required for determination of PCT is very small and the results can be available within 1 hour. This approach should result in earlier recognition of sepsis and initiation of adequate antibiotic therapy in all neonates with sepsis and thus improve their outcome and prognosis. More large multicentric studies are required for further studies of these markers which will reduce the rate of unnecessary antibiotic therapy. The limitations were the small size of both the study and control group. Also, Procalcitonin-LIA immunoluminometry is an expensive research tool and is available only in select tertiary care centers.

What is already known?

Procalcitonin and C- Reactive Protein are the most sensitive and specific markers of Neonatal Sepsis. Various markers have bee evaluated in the past on different sample populations at different times and settings. What this study adds? All biomarkers of neonatal sepsis have been evaluated together in a single study helping in better comparability amongst them.

TABLES AND FIGURES

TABLE-I

Total count	<5000cell/cmm or >20,000cell/cmm
Absolute neutrophil counts (ANC)	<1750 cells/cmm
Absolute band count	>2000 cells/cmm
I:T	> 0.2
Toxic granules	Presence
Micro ESR	>15 mm in first hr
CRP	> 10 mg/dl
Procalcitonin	> 2ng/ml

TABLE-II

Clinical criteria for diagnosis of Sepsis by Integrated Management of Childhood Illness (IMCI) [10]
Convulsions
Respiratory rate >60/min
Severe chest indrawing
Nasal flaring
Grunting
Bulging fontanel
Pus discharging from ear
Redness around the umbilicus extending to the skin
Temperature >37.7°C or <35.5°C
Lethargy or unconsciousness
Reduced movements
Not able to feed
Not attaching to the breast
No sucking at all
Crepitations
Cyanosis
Prolonged capillary refill time

TABLE III- Distribution of Neonates according to diagnosis

Investigations	Neonates with Proven sepsis	Neonates with Probable sepsis	Neonates with No sepsis
TC			
<5000cells/cmm	2 [6.25%]	2 [5.88%]	0 [0%]
>5000cells/cmm	30 [93.75%]	32 [94.11%]	19 [100%]
ANC			
<1750cells/cmm	0 [0%]	2 [5.88%]	0 [0%]
>1750cell/cmm	32 [100%]	32 [94.12%]	19 [100%]
ABSOLUTE BAND COUNT			
>2000/cmm	11 [34.38%]	6 [17.65%]	0 [0%]
<2000/cmm	21 [65.62%]	28 [82.35%]	19 [100%]
MICRO ESR			
>15mm/hr	9 [28.13%]	1 [3%]	0 [0%]
<15mm/hr	23 [71.87%]	33 [97%]	19 [100%]
I:T RATIO			
>0.2	9 [28.13%]	6 [17.65%]	0 [0%]
<0.2	23 [71.87%]	28 [82.35%]	19 [100%]
PLATELET COUNT			
<1.5 lac	18 [56.25%]	4 [11.8%]	0 [0%]

>1.5lac	14 [43.75%]	30 [88.2%]	19 [100%]
CRP			
>10mg/dl	29 [90.63%]	16 [47.06%]	0[0%]
<10mg/dl	3 [9.37%]	18 [52.94%]	19 [100%]
PCT			
>2ng/ml	29 [90.63%]	9 [26.47%]	5 [26.31%]
<2ng/ml	3 [9.37%]	25 [73.53%]	14 [73.69%]

TABLE IV- Statistical analysis of various Diagnostic tests

INVESTIGATIONS	SEN(%)	SPEC(%)	PPV(%)	NPV(%)	ACC(%)
TLC	6	96.2	50	3	62.3
ANC	6.2	96.2	100	62.9	62.3
Toxic granules	28.1	62.2	31	58.9	63.5
ABC	34.3	88.6	64.7	30.8	68.2
I:T	28.1	64.1	32	59.6	50.5
Mic ESR	28.1	98.1	90	69.3	71.7
PLT	56.2	84.9	69.2	76.2	74.1
CRP(>10mg/dl)	90.6	69.8	64.4	92.5	77.6
PCT(>2ng/ml)	90.6	83	76.3	93.6	85.8

(SEN= Sensitivity, SPEC=Specificity, PPV= Positive Predictive Value, NPV= Negative Predictive Value, ACC=Accuracy)

TABLE V- Mean values of the markers studied

MEAN values	CRP (mg/dl)	PCT (ng/ml)	I:T	PLT (lakh/r)	ESR (mm/hr)	BAND COUNT (Cells/cmm)	TC (Cells/cmm)	ANC (cells/cmm)
PROVEN SEPSIS	44.77	32.6	0.17	1.93	11.85	1939	15715	9806
PROBABLE SEPSIS	15.85	2.07	0.17	2.61	9.47	1232	12529	7446
NO SEPSIS	5.81	0.61	0.12	1.89	9.52	701	11863	6463
Pvalue	< 0.0001	< 0.0001						

TABLE VI- Comparison with other studies

STUDY (YEAR)		SAMPLE SIZE	SENSITIVITY	SPECIFICITY
Chiesa et al (2003)[24]	CRP	219	89%	87%
	PCT		74%	89%
Blommendahl et al.(2002)[27]	PCT	169	77%	84%
	CRP		58%	64%
Boo NY et al (2008)[28]	PCT	87	88.9%	65.2%
	CRP		55.6%	89.9%
Lapillone et al (1998)[29]	PCT	150	84%	91%
	CRP		28%	97%
Monneret et al(1997)[25]	PCT	88	86%	100%
	CRP		46%	97%
Engux et al (2001)[17]	PCT	46	99%	89%
	CRP		96%	84%
Our study (2015)	PCT	85	90.6%	69.8%
	CRP		90.6%	83%

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