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ORIGINAL ARTICLE

Evaluation of Procalcitonin and Presepsin in prediction for early onset neonatal sepsis.

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ABSTRACT… Objective: To determine the presepsin and procalcitonin significance in cord blood and compare with lactate and C-Reactive protein for early prediction of neonatal sepsis. **Study Design:** Case Control Study. **Setting:** Military Hospital Rawalpindi. **Period:** Sep 2018 to July 2019. **Methods:** Mothers, having deliveries with early or prolonged rupture of membrane, preterm, dai handled, meconium and failure of induction have been included. Out of 60 neonates, nineteen were cases with a clearly documented suspicion of sepsis and confirmed by neonatologists, remaining were control. Mean and Standard Deviation were calculated. The difference in all biochemical markers levels among case and control groups were assessed by independent t-test. Sensitivity, specificity, accuracy, and predictive value of both markers were calculated by medcalc diagnostic calculator. Regression analysis to access the strength. Receiver Operating Characteristics curve for most accurate cut off values and Area Under the Curve was calculated. **Results:** Independent sample t test revealed the strong association of procalcitonin and presepsin with neonatal sepsis. Presepsin has higher positive predictive value 83.33% and negative predictive value 90.48% with 88.33% accuracy while procalcitonin has positive predictive value 62.50%, negative predictive value 88.89% and accuracy 78.33%. Stepwise regression analysis showed better in combination than single in predication of neonatal sepsis. The cutoff value for procalcitonin was 0.4ng/ml (AUC of 84.5%.) and for presepsin was 305pg/ml (AUC of 86.5%). **Conclusion:** In comparison to lactate and CRP, a prediction model that incorporates two biochemical indicators, procalcitonin and presepsin, can reduce infant mortality and morbidity by spotting neonatal sepsis early.

Key words: Cord Blood, C Reactive Protein, Early Onset Neonatal Sepsis, Presepsin, Procalcitonin, Sepsis.

INTRODUCTION

The clinical appearances are variable and nonspecific so to reach at an appropriate definition of sepsis, there have been three consensuses since 1991. According to International Sepsis Definition Conference 2014, Sepsis - a clinical syndrome that shows the presence of both infection and systemic inflammation. In 2016, updated criteria of sepsis were stated by ESICM (European Society of Intensive Care Medicine) and SCCM (Society of Critical Care Medicine) consensus task force that life threating organ dysregulation brought about by host response failure to infection.[1] This new definition closely reflects everyday clinical language for sepsis and this third time consensus (sepsis 3) definition clearly differentiate bad infection from uncomplicated conditions.[2] Neonatal Sepsis may be early-onset or late-onset. In early onset neonatal infections, 85% of EONS occurs within 24 hours, 5% present between 24-48 hours, and a smaller percentage present between 48-72 hours(2) LONS develops after 3 days of life. A study in United Kingdom has shown that 50% of neonatal sepsis mortalities occur in first 24 hours and half of these neonates die before transfer to NICU.[3] Early onset neonatal sepsis is the third leading cause of mortality in developing countries within first 72 hours after birth where mortality rate in neonatal sepsis is as high as 60%. and 1.6 million/year neonates die in these countries. In Pakistan, a study reported that the mortality rate is 78 neonatal deaths (range 78-100)/1,000 live births.

The neonates can get the pathogens either in utero or intrapartum.[4] Maternal as well as neonatal

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factors can cause EONS (Table-I).

In neonatology, it is challenging to enable clinicians for early screening, timely diagnose of neonatal sepsis[5] because of small amount of blood from neonates. For neonate venipuncture expert hands are required so sampling take too much time for enough blood volume. Cord blood is the first available sample which help the clinician to start therapeutic strategy as soon as possible[6] Cord blood in sepsis would spare the infant a painful and invasive procedure, reduce the mother stress, ample amount of blood is available for biomarkers and culture.[7] Noninvasive prognostic tools used to assess the risk of neonatal sepsis include measurement of cord blood CRP, lactate, procalcitonin, but these predictable infection markers, when used alone, have poor diagnostic value in distinguishing neonates with sepsis from those with lower risk of infection.[8] In pediatrics, the most frequently employed biomarker is the CRP, which, however, is highly non-specific and has an unfavorable kinetic. Its level increases within 6-10 hours in neonates after exposure to infectious agent and peaks at 2-3 days so unreliable in early onset neonatal sepsis. High levels of lactate in the blood point to acute or chronic cell damage[9], but additional tests are necessary to discover its cause. Procalcitonin is prime biomarker which start to rise in early sepsis. Early rise PCT levels in neonatal sepsis (reach its peak within 2-4 hours) makes it a good marker for early diagnosis of sepsis in neonates.[10] Its levels are helpful in prediction of severity of infection and response to treatment Presepsin as predictor of early EONS in umbilical cord blood of premature with PROM. Its levels increase in blood within two hours after infection and reach at peak within 3hours[11] in adult patients and returns to baseline concentrations after 4–8 hours. It is also known as minor acute phase reactant because directly secreted by hepatocytes. Presepsin as compared to CRP and procalcitonin showed greater diagnostic value.[12] It is fast, bed side and convenient method to access the sepsis and best in diagnostic and prognostic purposes. Hence it can be used as predictive marker for neonatal sepsis. This study was carried out to clarify debated data, to integrate the limited research dealing with the role of presepsin in neonatal sepsis and to support the introduction of this novel inflammatory biomarker presepsin with procalcitonin in the clinical practice.

The aim of this study was to analyze the relationship between presepsin with neonatal sepsis and procalcitonin and to compare these two biomarkers with routinely used systemic inflammatory biomarkers: Serum C reactive protein and lactate in neonates.

METHODS

This Case Control study was conducted in Army Medical College and Military Hospital Rawalpindi from Sep 2018 to July 2019 after approval of ethical review committee 27/2/2019. Consecutive sampling was done. 60 sample size was taken by using WHO calculator. Those mothers, having deliveries with early rupture of membrane, prolonged rupture of membrane, preterm, dai handled, meconium and failure of induction have been included. In 60 neonates of both sexes, which were susceptible to EONS, nineteen were taken as cases with continuous clinical unsteadiness and clearly documented suspicion of sepsis, confirmed sepsis by two neonatologists and being admitted in NICU within 1-3 days of life. While remaining were control who have no infection.

A sample of 5ml cord blood was taken in plain tube and 2ml in sodium fluoride/ calcium oxalate tube for plasma lactate levels. All the samples were centrifuged after clotting. Lactate was processed and remaining separated sera was stored at -20OC in Eppendorf tubes prior to analysis. Plasma lactic acid was measured by photometric lactate oxidase enzymatic method on Selectra pro XL. Serum quantitative level of C-reactive protein (CRP) was performed on Roche Diagnostics analyzer (Roche Cobas e501). While procalcitonin measured by a Cobas e411 analyzer (Roche Diagnostics, Mannheim, Germany) and presepsin which was estimated by enzyme immunoassay manually following manufacturer specified guidelines. Statistical analysis was done by using SPSS software version 20. Mean and Standard

Deviation (SD) was calculated to assess the level of lactate, CRP, procalcitonin and presepsin. The difference in the level of all biochemical markers among the case groups and control groups were assessed using independent t-test. Sensitivity, specificity, accuracy, and predictive value of procalcitonin and presepsin was calculated by medcalc diagnostic calculator. To access the strength of predictive markers, procalcitonin and presepsin regression analysis was applied. Receiver Operating Characteristics (ROC) curve was drawn and Area Under the Curve (AUC) was calculated and compared and the most accurate cut-off values were taken to predict sepsis.

RESULTS

In case of chemical biomarkers, Lactate showed low levels 4.66±3.17 mmol/L in cases, 6.38±4.76 mmol/L for control, and statistically insignificant (p=0.16) and CRP values were 3.18±12.08 mg/L and 5.38±23.93 mg/L in cases and controls respectively, and it was also insignificant in septic cases and controls (p=0.65). Both these routinely used biomarkers showed insignificant results in prediction of early onset neonatal sepsis. Procalcitonin has mean 0.968±0.13 for cases and 0.0288±0.0176 for controls, p value <0.05 and presepsin 570.58±342 and 143.50±251 respectively for cases and controls, p value <0.05.

	Case		Control		
	Mean	SD	Mean	SD	P-Value
Lactate	4.66	3.17	6.38	4.76	0.157
CRP	3.18	12.08	5.80	23.93	0.655
Procal-citonin	0.0968	0.13462	0.0288	0.01763	0.002
Presep-sin	570.58	342.38	143.50	251.97	<.001

Table-I. Lab Values of the biomarkers & Independent Samples Test

For sensitivity & specificity of PCT and Presepsin, 2x2 table taken at cut off PCT 0.4ng/ml and Presepsin 305pg/ml. Presepsin has higher positive predictive value 83.33% (80.08-98.46) and negative predictive value 90.48% (79.84-95.80) with 88.33% accuracy. For procalcitonin, positive predictive value 62.50%, negative predictive value 88.89% and accuracy 78.33% which is less than presepsin.

	Sepsis	
Procalcitonin	Present	Absent
Positive	15	9
Negative	4	32
	Sepsis	
Presepsin	Present	Absent
Positive	15	3
Negative	4	38

Table-II. Procalcitonin and Presepsin Showing True Positive, False Positive, False Negative and True Negative

	Procalcitonin		Presepsin	
	Value	95% CI	Value	95% CI
Sensitivity	78.95%	54.43-93.95%	78.95%	54.43-93.95%
Specificity	78.05%	62.39-89.44%	92.68%	80.08-98.46%
Positive Predictive Value	62.50%	47.22-75.64%	83.33%	62.14-93.84%
Negative Predictive Value	88.89%	76.74-95.10%	90.48%	79.84-95.80%
Accuracy	78.33%	65.80-87.93%	88.33%	77.43-95.18%

Table-III. Sensitivity, Specificity, PPV, NPV and Accuracy of Procalcitonin and Presepsin

The strength of the prediction of a marker can be evaluated by comparing the values of R2, greater the value, better is the prediction. Similarly, lesser Standard error of estimate means predictability is more reliable.

Regression equations:

Risk of infection= (-0.798) procalcitonin+(-0.001) presepsin+1.918

Risk of infection= (-0.001) presepsin+1.904

Risk of infection= (-2.216) procalcitonin+ 1.795

	R^2	Std. Error of Estimate
Combined	0.352	0.3840
Presepsin	0.337	0.3851
Procalcitonin	0.316	0.4359

Table-IV. Regression analysis of presepsin & procalcitonin

By using this regression fit model, we can conclude that combining both markers for

predication of neonatal sepsis is a better strategy.

Stepwise regression analysis shows that combination of both the markers for use of predication of neonatal sepsis is better than a single biomarker. The cutoff of PCT was calculated to be 0.04ng/ml with a CI of 95% (71.9%-97.1%), with an AUC of 84.5%. Similarly, cutoff of presepsin was determined to be 305pg/ml with a CI of 95 (75.5%-97.4%) with an AUC of 86.5% at sensitivity and specificity.

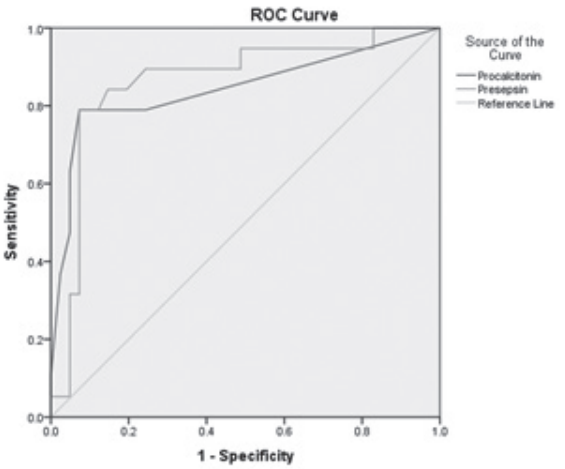

Figure-1. ROC Curve for Procalcitonin & Presepsin

DISCUSSION

Early-onset neonatal sepsis (EONS) is an alarming condition responsible for an important portion of neonatal morbidity and mortality. EONS is vertical transmission, so its mortality rate is high. Different criteria have been established for early detection and diagnosis of sepsis but there is still need for international consensus to define this uncertainty in diagnosis of neonatal sepsis. In the absence of proper diagnostic tools, most neonates treated with antibiotics as a case of presumed sepsis. This study compared the performance of currently used inflammatory markers to predict the neonatal infection in all suspected neonates. Fetal lactate levels are not influenced by maternal factors or by the uteroplacental lactate production except fetus himself.[9] Some studies found no significant correlation between umbilical cord blood lactate whereas others found a positive weak correlation. Our studies have shown no significant relation between early onset neonatal sepsis and lactate. The statistically significance in neonates with sepsis and non-septic was 0.157 which is insignificant. CRP, an acute phase peptide synthesized by the liver in response to infection in neonates, was shown to be the best diagnostic marker of neonatal sepsis. However, it presents a low sensitivity during the early hours of neonatal life because it needs 6 hours to release and need 10-12 hours to response in infection.[13] CRP aids in diagnosis of sepsis in some conditions but its levels also raised in the following conditions: late pregnancy, acute bacterial and viral infections and old age. The specificity of CRP in diagnosis and progression of sepsis has never been proven. CRP is increased from 45% to 97% during progression of infection.[14]

The diagnostic properties of procalcitonin are better than that of CRP when measured in cord blood of suspected neonates.[15,16] Hence, we observed a threshold value between 0.5 and 1 ng/mL, whereas other study suggested the higher threshold values. A cut off value of PCT 0.071 ng/ml shows best sensitivity and moderate diagnostic accuracy and predictive value in neonatal sepsis.[17] Therefore, procalcitonin has been known as a reliable biomarker that has added significance i.e. assist in diagnosis, evaluate prognosis, and contribute in treatment selection and monitoring.[18,19] This biomarker is now widely used in clinical laboratories in Europe and USA with FDA recommendation for the evaluation of occurrence, diagnosis and monitoring of sepsis. Meisner et all and Cetin et all findings are consistent with finding in this study. At cut off 0.4ng/ml, Procalcitonin had sensitivity of 78.95% and specificity of 78.05% and moderate diagnostic accuracy.

Presepsin (CD 14) is most suitable marker for the severity as well as prognosis of sepsis in early neonatal period. Cutoff value of 400 pg./ml was predictive of neonatal sepsis in different studies.[20,21] Its bedside importance is proved by many studies.[22,23] At cutoff value of 672 pg/ml, presepsin had sensitivity and specificity of 97% and 98% respectively making it more sensitive and specific for prediction of neonatal sepsis.[24,25] Our studies showed sensitivity of presepsin was 78.65% and specificity was 92.68 at cut off

305pg/ml. The difference in serum concentration of Presepsin between cases and controls would be at least 220 ng/l.[26,27] This value is correlated with finding in our study in which difference between controls and cases is >224ng/l. The AUC was 0.865 (95% CI 0.755–0.974), indicating an incomparable characteristic of presepsin to measure the diagnostic value for sepsis in our results. Sensitivity of presepsin was 78.65% and specificity was 92.68%. These values although encouraging, but they may not convince neonatologist to use this single biomarker in the prediction of early neonatal sepsis.

Different studies showed that in ROC analysis, AUC value of PCT was 59.9%, p=0.15.[12] For presepsin to be used for detection of early occurrence of sepsis the value of the AUC was higher 75.8%, hence proving that it is better and ideal biomarker for early diagnosis of neonatal sepsis. Presepsin is not secreted in response to any physiological stimulus and is directly produced by LPS-CD14 complex into the circulation and hydrolyzed by plasma protease and is secreted by monocytes after phagocytosis. In comparison to presepsin, PCT could be directly activated by the toxin and affected indirectly by proinflammatory compounds such as IL-1b, IL-6 and TNF-α. PCT levels could be increased in conditions of stress, such as trauma or surgery in absence of any bacterial infection.[12,20] The combining strength of procalcitonin and presepsin in our study was proved by comparing the values of R_2, which showed greater value (0.352) so proved its diagnostic value. Similarly, lesser standard error of estimate means predictability is more reliable. Presepsin has higher positive predictive value 83.33% (80.08-98.46) and negative predictive value 90.48% (79.84-95.80) with 88.33% accuracy. For procalcitonin, positive predictive value was 62.50% whereas negative predictive value was 88.89% with 78.33% accuracy which is less than presepsin.

In critical illness guide therapy, multiple biomarkers have been used to differentiate between infective and non-infective causes. Routinely used biomarker, lactate, shows association irrespective of underlying pathology hence it is not reliable biomarker in sepsis. CRP is a traditional biomarker used in diagnostic criteria of sepsis, but it is a marker of late onset neonatal sepsis and has more prognostic value. PCT then replaced CRP which was deemed specific in early sepsis. The biological role of presepsin in the host-pathogen response[23,24] and its diagnostic value along with procalcitonin has been reviewed by regression analysis.

Developing different algorithms to predict the occurrence of sepsis in susceptible neonates are useful for screening of all neonates and infants in developing countries. Primary step would be to save the cord blood of high-risk mothers. Cord blood can be used for culture and then to isolate the causative bacteria when enough postnatal blood samples for culture may not available. This simple cord blood analysis can be possible even at any primary care setting in developing countries. Second step is asking for two signs out of several lifesaving signs i.e., temperature variability, heart rate ≥180 beats/min or ≤100 beats/min, respiratory rate instability, lethargy/ altered mental status, feed intolerance, systolic blood pressure of 100 mmHg or less etc. By using only two signs for prediction of neonatal sepsis results in a substantial loss of sensitivity, about one-half of the children with confirmed bacterial infection thus can be missed. Third step is on cord blood of neonates having positive early signs, different lab tests should be performed, e.g. procalcitonin which is already in use and emerging marker, presepsin.

LIMITATION

Since it is a single center study, further multi center studies with large sample size are warranted before adopting the above recommended protocols / algorithm in routine clinical practice.

CONCLUSION

It is concluded from this study that a prediction model can be formulated incorporating two biochemical markers e.g. PCT & Presepsin for early detection of neonatal sepsis. This study also strongly suggests, as evaluated through both statistical analysis & clinical correlation that PCT and Presepsin in combination with lactate

and CRP, gives better results for early detection of neonatal sepsis as compared to single use of these biochemical markers.

RECOMMENDATION

By establishing these algorithms and incorporating them into routine protocols leads to early risk stratification, hence decreasing the mortality and morbidity in neonates.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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3	Tariq Mahmood	Contribute to the conception, Design.	Tariq Mahmood
4	Amna Saddique	Analysis, Simple collection.	Amna Saddique
5	Nadia Ambreen	Interpretation.	Nadia Ambreen
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