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Original Article

Incidence, Risk Factors and Role of Sepsis Screen in Diagnosis of Sepsis in Newborn Admitted in NICU, Teerthanker Mahaveer Hospital, Moradabad

Vivek Tyagi[1], Utkarsh Sharma[2], Khushboo Malhotra[3], Sumit Goel[4]

[1.3.4]Post graduate student, [2]Professor and head, Department of Paediatrics, Teerthanker Mahaveer Hospital, Moradabad, U.P., India

ABSTRACT:

Aim of the study: To assess the role of Mean Platelet Volume and serum uric acid levels as additional markers for the diagnosis of Neonatal Sepsis. **Materials and Method:** The present hospital based study was carried out in the Neonatal Intensive Care Unit, Teerthanker Mahaveer Hospital, Moradabad to assess the role of Mean Platelet Volume and serum uric acid levels as additional markers for the diagnosis of Neonatal Sepsis. Blood was drawn from the infants, who had clinical signs of sepsis, from peripheral vein under strict aseptic precautions for evaluation of TLC, C-reactive protein (CRP), micro-ESR, MPV and serum uric acid was sent and analysed for case and MPV and URIC ACID was analysed for control group. The software used for the statistical analysis were SPSS (statistical package for social sciences) version 21.0. The statistical test used was Unpaired or Independent t-test for comparison of mean value between 2 groups. **Results:** The mean Platelet Volume was significantly more among Neo-natal sepsis patients (10.29±1.23) than non-sepsis patients (9.12±1.07).The mean Serum Uric Acid among Neo-natal sepsis patients was 4.01±0.11 and among non-sepsis patients was 3.54±0.55 with no significant difference. **Conclusion:** MPV is a simple laboratory investigation. In this study we found that neonates with sepsis had higher MPV levels with no difference in the serum uric acid levels.

Key words: C-reactive protein, Mean Platelet Volume, Neonatal Sepsis, Serum Uric Acid.

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Corresponding Author: Dr. Vivek Tyagi, Post graduate student, Department of Paediatrics, Teerthanker Mahaveer Hospital, Moradabad, U.P., India

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INTRODUCTION

Neonatal sepsis is a clinically represented by symptoms of infection with or without bacteremia in first month of birth.1 Incidence of neonatal sepsis according to data from national neonatal perinatal database is 30 per 1,000 live births.[1]

Neonatal septicemia remains one of the main causes of mortality and morbidity despite the progress in hygiene, introduction of new and potent antimicrobial agents for treatment and advanced measures for diagnosis. Nearly 10%,infants have infections in the first month of birth resulting in 30to50% of total neonatal deaths in developing countries.[2] These neonatal deaths are due to infection, birth asphyxia and as a result of premature birth and low birth weight.[3]

The prevalence of neonatal bacterial sepsis is variable from country to country as well as within the same country. In developing countries, neonatal mortality results from all expected causes of neonatal sepsis, consequently, it is about 34 per 1000 live births, occurring mainly in the first week of life as compared to 5 per1000 live births in developed countries.[4]

Neonatal sepsis is grouped into 2 categories depending on the arrival of Symptoms. Early sepsis starts in early 72 hours. Infants who have EOS have clinical symptoms like respiratory distress & pneumonia source of infection being maternal genital tract whereas Late Onset Sepsis presents after 72 hours of life. The infection of LOS is nosocomial or community acquired.[5]

The risk factors related with an increased risk of early onset sepsis:[5]Low birth weight (<2500 grams) or prematurity, Febrile illness in the mother having bacterial infection within two weeks before delivery, Foul liquor, Membranous ruptures > 24 hours, Single unclean or> 3 sterile vaginal examination during labor, stretched labor (sum of 1st and 2nd stage of labor≥ 24 hrs) and Perinatal asphyxia (Apgar score <4 at 1 minute).[5]

Certain clinical symptoms like difficulty in breathing, hypothermia, tachypnea, grunting, lethargy, and vomiting of an infant puts the clinician to look about

EOS. These findings may be differentially diagnosed with non-infective causes because they are not specific for EOS.[6] At this point serum biomarkers have been proposed as being useful indicators for early identification of septic infants.[7]

Biomarkers can have an important place in this process because they can indicate the presence or absence or severity of sepsis,[8,9] and can differentiate bacterial from viral and fungal infection, and systemic sepsis fromlocal infection. Biomarkers include roles in prognosis, antibiotic therapy, therapy response and recovery from sepsis, differentiating Gram-positive from Gram negative microorganisms as the cause of sepsis, predicting sepsis complications and the development of organ dysfunction (heart, kidneys, liver or multiple organ dysfunction). Still role of biomarkers in therapy of septic patients remains undefined.[10]

Many biomarkers have been reported to be valuable to predict the disease before clinical manifestations occurring in the literature.[11,12] But the common characteristics of these are that they are either examining the infants of high-risk mothers or have examined infants with suspicious clinical findings. In a case control study of 145 patients with sepsis and143 controls, Guclu showed that, MPV and PDW were useful in diagnosis of sepsis and patients with PDW of morethan 18% have a higher risk of death.[13]

Thrombocytopenia occurring in critically ill patients isthe result of hemodilution, increased platelet consumption, increased platelet destruction (immune mechanisms)[14] and increased platelet sequestration.[15] Septicemia related destruction of platelets increases production and release into the peripheral blood of larger and younger platelets.[16] leading to bone marrow suppression.[13]

Platelet volume indices, estimated by automated blood cell analysers, show the changes that accompany the alterations in platelet counts.[17] Platelet parameters such as MPV and PDW (reflection of the variation of the platelet size in the circulation[18] have been routinely available to the clinicians for some time. However, their significance in various platelet disorders have only been studied recently.[13]

Nelson and Kehl reported that in acuteinfection, there was platelet consumption and it was associatedwith an increase in MPV.[19]Becchi et al[20]notedthat MPV at an early stage of sepsis was important prognostically. MPV increased during the admission periodin those who died, compared to survivors. In neonateswith sepsis, a low platelet count and an increase in MPVhas been observed by Guida et al.[21]Patrick et al demonstratedthat neonates with late onset sepsis (bacteremiaafter 3 days of age) had a dramatic increase in MPV andPDW.[22]

Previous studies have evaluated UUA/Cr ratio as a predictor of mortality and severity of diseasein perinatal asphyxia, and have established the correlationbetween the Apgar score and the urinary uric acid tocreatinine ratio.[23]Moreover, rising of serum uric acid asa predictor of mortality in critically ill children has alreadybeen reported.[1]

Mean platelet volume (MPV) and uric acid are coming up as additional markers for diagnosis of neonatal sepsis several studies have shown both in India and abroad showing there significant role in sepsis as upcoming diagnostic marker.

MATERIALS AND METHOD

The present hospital based study was carried out in the Neonatal Intensive Care Unit, Teerthanker Mahaveer Hospital, Moradabad to assess the role of Mean Platelet Volume and serum uric acid levels as additional markers for the diagnosis of Neonatal Sepsis.

Method of collection of data:

The data was collected by a single examiner. The subjects were selected as per the following inclusion and exclusion criterias:

Inclusion criteria:

a) Neonates with birth weight >1.5kgs of either gender.
b) Those parents &/ or accompanying relatives willing to give written informed consent.

Exclusion Criteria

a) Extremely low birth weight babies.
b) Neonates with surgical conditions
c) Post term neonates >42 weeks

PATIENT PRESENTING WITH ANY OF THE TWO RISK FACTORS FOR SEPSIS: The following risk factors seem to be associated with an increased risk of early onset Sepsis. 2,3

1. Low birth weight (<2500 grams) or prematurity
2. Febrile illness in the mother with evidence of bacterial infection within two weeks prior to delivery
3. Foul smelling liquor
4. Rupture of membrane >24 hour
5. Single unclean or> 3 sterile vaginal examination during labor
6. Prolonged labor (sum of 1st and 2nd stage of labor >/=24 hrs)
7. Perinatal asphyxia (Apgar score <4 at 1 minute)

and/or clinical features of sepsis

- Hypothermia & fever
- Lethargy, poor cry and refusal to suck
- Poor perfusion, prolong capillary refilling time
- Brady/ tachycardia
- Respiratory distress, apnoea & gasping respiration
- Hypo/ hyper glycemia
- Metabolic acidosis

and positive sepsis screen with any of the two parameters positive in sepsis screen

Sampling and Analysis:

Blood was drawn from the infants, who had clinical signs of sepsis, from peripheral vein under strict aseptic precautions for evaluation of TLC, C-reactive protein (CRP), micro-ESR, MPV and serum uric acid was sent and analysed for case and MPV and URIC ACID was analysed for control group.

Information recorded
Maternal history, Birth history, Clinical examination, TLC, CRP, absolute neutrophil count, MPV, Micro ESR, I/T, serum uric acid level

Blood culture:
1-2 ml was collected in enriched media like Tryptican soya broth in proportion of 1:10.Then it is incubated at 37 °C, followed by subculturing on MacConkey's medium/Blood agar/ Chocolate agar every alternate day till 3 subcultures. Culture plates were examined every day for growth and reported within 48 hours along with the sensitivity pattern. Culture was taken negative if there was no growth for 3consecutivesubcultures.

C-Reactive Protein:
Value of >1 mg/dl, as determined by the rate nephelometry method, was defined as abnormally high.

Statistical analysis:
The software used for the statistical analysis were SPSS (statistical package for social sciences) version 21.0 and Epi-info version 3.0. The statistical test used was Unpaired or Independent t-test for comparison of mean value between 2 groups when the data follows normal distribution.

RESULTS

There were 53 (44.2%) males and 67 (55.8%) females in the present study. In Neo-natal sepsis group, we had 31 (44.3%) males and 39 (55.7%) females. In Non-sepsis group, we had 22(44.0%) males and 28 (56.0%) females.

The mean WBC count among Neo-natal sepsis patients was 18313.77±6989.98 and among non-sepsis patients was 8844.70±1124.46.The mean absolute Neutrophil Count among Neo-natal sepsis patients was 1478.16±459.66 and among non-sepsis patients was 5154.82±3413.25. The mean WBC count was significantly more among Neo-natal sepsis patients. The mean absolute Neutrophil Count was significantly more among Non- sepsis patients.(Table 1)

The mean Immature to total Neutrophil Ratio among Neo-natal sepsis patients was 0.26±0.04 and among non-sepsis patients was 0.14±0.02.The mean Immature to total Neutrophil Ratio was significantly more among Neo-natal sepsis patients.(Table 1)

The mean Platelet Volume among Neo-natal sepsis patients was 10.29±1.23 and among non- sepsis patients was 9.12±1.07.The mean Platelet Volume was significantly more among Neo- natal sepsis patients.The mean Serum Uric Acid among Neo-natal sepsis patients was 4.01±0.11 and among non- sepsis patients was 3.54±0.55.The mean Platelet Count among Neo-natal sepsis patients was 2.51 ±0.74 and among non- sepsis patients was 2.24±0.76. There was no significant difference in mean Platelet Volume between Neo-natal sepsis and Non-sepsis patients with no significant differencebetween them. (Table 2)

Among neo-natal sepsis patients, E. coli was found in 6 (8.6%), Enterobacter2 (2.9%), klebsiella pneumonia in 2 (2.9%), Pseudomonas in 2 (2.9%), S. aureus in 3 (4.3%) andSalmonella in 2 (2.9%) patients.Among neo-natal sepsis patients, 41 (58.6%) samples were positive for C-reactive protein.

Table 1: Mean WBC count and absolute-Neutrophil Count between Neo-natal sepsis and Non-sepsis patients

	Neo-natal sepsis		Non-sepsis				
	Mean	S.D.	Mean	S.D.	Mean Difference	t-test value	p-value
WBC count	18313.77	6989.98	8844.70	1124.46	9469.07	9.481	< 0.001*
Absolute Neutrophil Count	1478.16	459.66	5154.82	3413.25	-3676.66	-8.914	< 0.001*
Immature to total Neutrophil Ratio	0.26	0.04	0.14	0.02	0.12	18.291	< 0.001*

Unpaired t-test *** Significant difference**

Table 2: Mean Platelet Volume between Neo-natal sepsis and Non-sepsis patients

	Neo-natal sepsis		Non-sepsis				
	Mean	Std. Deviation	Mean	Std. Deviation	Mean Difference	t-test value	p-value
Mean Platelet Volume	10.29	1.23	9.12	1.07	1.17	5.429	< 0.001*
Serum Uric Acid	4.01	0.11	3.54	0.55	0.48	7.083	0.101#
Platelet Count	2.51	0.74	2.24	0.76	0.27	1.965	0.052#

Unpaired t-test *** Significant difference** **# Non-significant difference**

DISCUSSION

Early onset neonatal sepsis, mostly remarkable in the developing countries, is a major cause of morbidity and mortality of infants.[24]Early diagnosis and adequate theory of the infected neonates play a vital role in lowering such mortality and morbidity rates.[7] The best known risk factors for EOS are chorioamnionitis and maternal systemic infections. Preterm birth and preterm rupture of membranes are also other risk factors for chorioamnionitis and EOS.[25]

Simple, rapid, non-invasive, and safe intrauterine infection detection tests can be useful in prediction of neonatal infection of babies of mothers either with or without active labor. If maternal infections during pregnancy are diagnosed and treated early, the mortality and morbidity of neonates due to EOS can be decreased. In the literature, several diagnostic methods of peripartum intrauterine infection detection have been considered. These can be listed as amniotic fluid cultures, serum procalcitonin, C-reactive protein (CRP) interleukin (IL)-6, IL-8, IL-10, IL-18, tumor necrosis factor-alpha (TNF-alpha), interferon gamma levelsetc.[26]

Mean WBC count

The mean WBC count was significantly more among Neo-natal sepsis patients. The mean absolute Neutrophil Count was significantly more among Non-sepsis patients.The mean Immature to total Neutrophil Ratio was significantly more among Neo-natal sepsis patients. This was quite in line with the study by Shalaby et al,[27]there were significant increase in WBCs count, I/T ratio and ANC in the patient group than in the control group.

Mean platelet volume

In our study, the mean Platelet Volume was significantly more among Neo-natal sepsis patients which was similar to the study by Guclu et al,[13]patients with severe sepsis have higher MPV compared to patients with sepsis. However, it concurred with other studies by Cekmez et al, Catal et al and Ahmed et al reporting that high fetal MPV levels may predict the EOS in preterm infants.[12,28,29]These results are also valuable for early diagnosis of the disease of the neonates.

The study by Guclu et al,[13] showed that greater MPV levels higher than 8 fl have moderate (53.47 %) sensitivity and good (87.41%) specificity for sepsis diagnosis. Therefore, MPV may be used as an auxiliary test in the diagnosis of sepsis. A high positive predictive value of this test (81.1 %) supports this hypothesis too. Moreover, in multivariate logistic regression analysis, the independent laboratory parameters in sepsis diagnosis were MPV OR:2.05 (1.5 – 2.7)and PDW OR:1.8 (1.3 – 2.5).

It has been demonstrated that coagulation and platelet activation/hyper aggregation can occur in an early phase of sepsis.[20]In order to obtain a larger surface, platelets change their discoid shape to a spherical shape during activation. At the same time, pseudopodia formation occurs. Platelets with increased number and size of pseudopodia may affect the PDW.[16] Platelet volume is related to platelet function and activation as well. Generally, platelet production increases as platelet count decreases. An increased number of young platelets is also functionally more active than olderplatelets.[30]

The low levelof thrombocytopenia in patients with severe sepsis can explain the high levels of MPV and PDW. Van Der Leile et al[31]have shown an increase in MPV in septicemic patients. He postulated that with sepsis there is increased thrombocytosis and this result in increase in the megakaryocyte ploidy and an increase in MPV.

Mean serum uric acid levels

In our study, the mean Serum Uric Acid (SUA) was not significantly more among Neo- natal sepsis patients. This was similar to the study by Hooman et al.,[1] showed that higher SUA levels served as an additive risk factor in sepsis.

These study findings did not agree with findings by Shalaby et al,[27]demonstrated that SUA levels were significantly lower in patients with sepsis, Aydin and his colleagues[5] compared 146 cases of NS with 142 healthy newborns and found that the newborns withsepsis had lower SUA levels.

Chen et al.[32] reported that the urinary UA/Cr ratio was quite higher in hypoxic premature infants than in hypoxic term infants. Bahubali et al.[33] reported that this ratio was elevatedin neonates with birth asphyxia and was correlated significantly with the clinical severity of the disease. They also reported significant negative correlation between this ratio andthe Apgar score, which was also indicated in studies by Banupriya[34]and Bhongir.[35]

Generally uric acid increases due to its more production and less excretion. Everything is interrelated as septic shock leads to hypoxia of multiple organs which further increases the change in xanthine/hypoxanthine to uric acid through activation of xanthine oxidase in microvascular endothelium,[36] thus uric acid settles endothelium of vessels, the release of vasorelaxation factors is hampered,[37,38] and Interfering contraction leading to mainly kidney dysfunction

Mean platelet count

In our study, the mean Platelet Count among Neo-natal sepsis patients was 2.51±0.74 and among non-sepsis patients was 2.24±0.76with no significant difference between them. This was similar to the study by Guclu et al,[13] patients with severe sepsis have lower platelet count compared to patients with sepsis.

Findings in a recent study support our results. In thatstudy, low platelet count was found in the first three days of Gram-positive septic patients and in the firstfour days of Gram- negative sepsis.[39]Moreau et al[40]found that on the receiver operating characteristic curve, the platelet count decline of 28.3% was associated with the best discrimination between survivors and non survivors. Thirty seven percent of those who died had a decline of

more than 28.3%whereas 20.9% of survivors had this platelet decline.

Thrombocytopenia was associated with longer ICU stays, a higher incidence of bleeding events, greater transfusion requirements and higher mortality.[6,40]But somehow, sepsis is associated with more level of platelet count.[41]

Bacterial culture

The clinical signs and symptoms of neonatal sepsis are subtle and non-specific, making its early diagnosis difficult, and it can interfere with other life-threatening diseases, such as necrotizing enterocolitis and perinatal asphyxia.[42,43] Blood culture is still the gold standard for definitive diagnosis of neonatal sepsis, in spite of some drawbacks of blood cultures as being time consuming, low sensitivity, and possible contamination especially with commensal CoNS that could be produced.

Bacterial culture was found to be positive in 17 (24.3%) samples only withE. coli to be predominant (8.6%) followed by S. aureus (4.3%) and Enterobacter, klebsiella pneumonia, Pseudomonas and Salmonella with 2.9% each among patients in our study.

C-reactive protein

Among neo-natal sepsis patients, 41 (58.6%) samples were positive for C-reactive protein in the current study. This was in line with the study by Naher and Khamael,[44]the results of C-reactive protein were positive in 33(66%) and 17(34%) were negative. This was in concurrence with the study by Shalaby et al,[27]CRP was significantly higher in cases than in controls, Hisamuddin et al,[45]Ganesan et al[46]andPark et al.[47]

The outcome of neonates with infections is based on the diagnosis and management. As a consequence, deciding whether to treat or not, balancing optimal patients care with aspects such as possible adverse events or antibiotic resistance, may be difficult. In line with this idea, there cognition of the risk factors for neonatal infections is extremely relevant in the clinical setting, since it contributes to the diagnostic reasoning and supports clinical decisions.[44]

As a limitation of this study we did not analyze multi variation and demonstration of MPV as an independent risk factor for sepsis diagnosis. Another limitation was a small number of patients. Further analyses are needed to determine a cut-off value for MPV in neonatal sepsis diagnosis.

CONCLUSION

The prevalence of EOS is more than LOS. 3 diagnostic parameters related to sepsis are Low birth weight, abnormal WBCs count and CRP. Enterobacter spp. and Klebsiellaspp. are responsible for neonatal sepsis.In conclusion we found that term infants with neonatal sepsis have higher MPV levels.

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