



STUDY OF VARIATION OF PLATELET DISTRIBUTION WIDTH & PLATELET LARGE CELL RATIO IN RELATION TO PLATELET COUNT IN NEWBORNS WITH SEPSIS, PROBABLE SEPSIS/SUSPECTED SEPSIS.

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ABSTRACT **Objective:** The present study was undertaken to evaluate the relevance of thrombocytopenia, platelet indices (PDW & P-LCR), C-reactive protein and blood culture in the early diagnosis of neonatal sepsis.

Methods: 100 neonates with predisposing factors or clinical suspicion of sepsis were enrolled in the study. 2 ml of blood was collected by peripheral venipuncture and sent to the pathology laboratory in EDTA vacutainers. Samples were processed in the Sysmex KX21 automated analyzers.

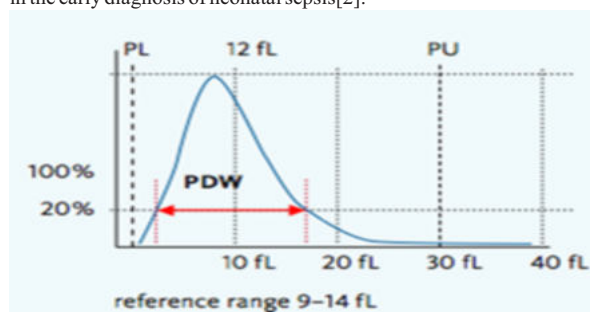
Results: Out of 100 neonates, 31 were suspected sepsis, 27 were probable sepsis & 42 were confirmed sepsis. 64% of infants with confirmed sepsis were preterm. Of the 100 neonates, 69 were males and 31 were females. Early onset sepsis was seen in 67% of the cases & late onset sepsis was seen in 33% of the cases. Caesarean section (66%), PROM (12.5%) and meconium aspiration (10%) were common maternal risk factors associated with neonatal sepsis. Among the 42 culture positive pseudomonas is predominant bacteria seen in 50% of cases, klebsiella seen in 28.5%, CONS in 16.7% & candida in 4.76%. In total of 100 patients 17 had thrombocytopenia out of which 11 were culture positive & were culture negative. Thrombocytopenia was in 50% of candida infection, 33.33% of klebsiella infection, 23.8% in pseudomonas infection & 20% of CONS infection. Severe degree of thrombocytopenia was seen in 29.4% of sepsis proven cases. Klebsiella pneumonia and pseudomonas aeruginosa were the most common Gram-negative organisms isolated. PDW & PLCR were inversely related to the platelet count. Out of 100 cases studied 10% had positivity for CRP.

Conclusion: Thrombocytopenia was seen more with late onset sepsis than early onset sepsis. Platelet indices values (PDW & PLCR) were inversely related to the platelet count. As these indices vary with bone marrow response & immune mediated destruction can be used in differentiating hypo productive & hyper destructive thrombocytopenia. Since CRP & blood culture take 1 to 2 days to be positive, Indices can be used on day 1 for early screening & prompt treatment even in small hospitals.

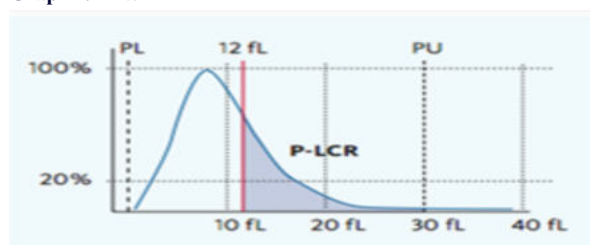
KEYWORDS :

INTRODUCTION

Systemic infection in neonates is accompanied with thrombocytopenia. Platelet indices are Mean platelet volume (MPV), Platelet distribution width (PDW), Platelet large cell ratio (PLCR) and Plateletcrit (MPV X platelet count). The PDW (Platelet Distribution Width) indicates the platelet distribution width measured at 20% relative height of the total height of the curve. An increased PDW is an indication for the anisocytosis of platelets. Standard PDW ranges from 9 to 14 fL. The P-lcr (Platelet Large Cell Ratio) indicates the percentage of large platelets with a volume > 12 fL. An increase of the parameter may be an indication for platelet aggregates, micro erythrocytes and giant platelets[1]. The present study was undertaken to evaluate the relevance of thrombocytopenia, platelet indices, C-reactive protein and blood culture in neonates as these parameters aid in the early diagnosis of neonatal sepsis[2].



Graph 1: PDW



Graph 2: PLCR

AIMS AND OBJECTIVES

- 1) To study the variation of PDW & P-lcr in neonatal sepsis.
- 2) To differentiate between hyper destructive and hypo productive thrombocytopenia.

MATERIAL & METHODS:

Study Design: Prospective study

Site: This study was conducted in a tertiary care center, Hyderabad from October 2013 to June 2014 in neonates with sepsis.

Sample: All neonates with sepsis, suspected sepsis/ probable sepsis admitted in NICU of Pragna children's hospital. A detailed clinical history of each patient was recorded.

After signing informed consent, 2 ml of blood was collected by peripheral venipuncture using aseptic precautions. The blood samples were sent to the pathology laboratory in EDTA vacutainers. Samples were processed in the Sysmex KX21 automated analyzers.

In a peripheral smear finding of 3 to 10 platelets per oil immersion field is normal (multiply this by 15000 to 20000 to get rough platelet count) Pathologist crosschecked more than 1% discrepancy then final platelet count was confirmed. Then after obtaining values correlation of the PDW & PLCR were studied.

Inclusion Criteria:

- 1) Neonatal age group (1-28 days) with sepsis & suspected/probable sepsis.
- 2) Newborns born to PIH mothers

Exclusion Criteria:

- 1) Dysmorphic babies with genetic causes of thrombocytopenia
- 2) Drug induced causes of thrombocytopenia

Statistical Analysis:

The quantitative parameters such as age and platelet indices, mean and median was computed and standard deviation was estimated as a measure of variation. The platelet count was grouped into mild, moderate and severe degree, normal & thrombocytosis Infectious status was divided as suspected sepsis, probable sepsis & confirmed

sepsis Prevalence of various organisms was confirmed by blood culture and correlated with thrombocytopenia and its indices.

RESULTS

The present study was conducted on 100 neonates (0-28 days) who clinically presented with symptoms of sepsis.

Designation Of Infection Status

Suspected Sepsis: is a new born with clinical signs & symptoms of sepsis.

Probable Sepsis: when clinical & laboratory findings (like increased TLC, increased Absolute neutrophil count, CRP positivity, immature/ total mature neutrophil count > 0.2) are consistent with bacterial infection but blood culture is sterile.

Confirmed sepsis: is one clinical & laboratory findings are consistent with bacterial infection along with blood culture positive.

42 out of 100 neonates were confirmed sepsis, 27 had probable sepsis and 31 were suspected sepsis. The statistical test used was ANOVA TEST. P value is 0.544, which is statistically insignificant, suggesting no significant co relation.

Age Distribution And Infectious Status

Majority of the cases were in the age group of 0 to 5 days out of which 24 were suspected sepsis, 20 were probable sepsis & 25 were confirmed sepsis. The statistical test used was ANOVA TEST. P value is 0.54, which is statistically insignificant, suggesting no significant co relation.

Infectious Status & Gender Distribution

Out of 100 cases 31 were suspected sepsis cases in which 19 were males & 12 were females respectively, similarly out of 27 cases of probable sepsis 16 were males & 11 were females respectively. In 42 with confirmed sepsis males were 24 & 18 were females. The statistical test used was ANOVA TEST. P value is 0.9399, which is statistically insignificant, suggesting no significant co relation.

Gestational Age With Infection Status

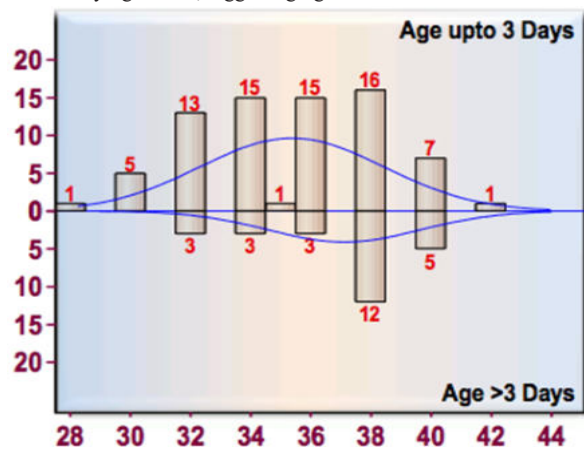
Out of 100 cases maximum number of cases (suspected, probable and confirmed sepsis) were below the age of 36 weeks. The statistical test used was ANOVA TEST. P value is 0.9399, which is statistically insignificant, suggesting no significant co relation.

Type Of Sepsis & Gestational Age

Early Onset Sepsis: Sepsis occurring within 72 hours of life.

Late Onset Sepsis: Sepsis occurring after 72 hours of life.

Out of 100 cases 73 were early onset sepsis & 27 were late onset sepsis. The statistical test used was ANOVA TEST. P value is 0.010, which is statistically significant, suggesting significant co relation



Risk Factors Or Perinatal Complications

Table 1. Risk Factors Or Perinatal Complications

	SUSPECTE D SEPSIS	PROBABL E SEPSIS	CONFIRME D SEPSIS	TOTAL
CESEAREAN	23	17	28	68
PROM	4	6	5	15

MECONIUM	2	4	4	10
PIH	3	2	7	12

The statistical test used was ANOVA TEST. P values were above 0.05, which were statistically insignificant, suggesting no significant co relation.

Blood Culture Positivity And Type Of Sepsis

Out of 100 cases 42 were culture positive and 58 were culture negative. Among the culture positive pseudomonas is predominant bacteria seen in 50% of cases, klebsiella seen in 28.5%, CONS in 16.7% & candida in 4.76%. Culture positivity is seen more in early onset sepsis than late onset sepsis. The statistical test used was ANOVA TEST. P value is 0.030, which is statistically significant, suggesting significant co relation

Platelet Count Variation In Relation To Infection Status

Out of 100 cases studied 17 had thrombocytopenia, 3 had increased platelet count, rest others had normal platelet count. Severe degree of thrombocytopenia was seen in 29.4% of sepsis proven cases. The statistical test used was ANOVA TEST. P value is 0.104, which is statistically insignificant, suggesting no significant co relation.

Variation Of Platelet Count With Different Organisms

In total of 100 patients 17 had thrombocytopenia out of which 11 were culture positive & 6 were culture negative. Thrombocytopenia was in 50 % of candida infection, 33.33 % of klebsiella infection, 23.8% in pseudomonas infection & 20% of CONS infection. The statistical test used was ANOVA TEST. P value is 0.09, which is statistically insignificant, suggesting no significant co relation.

CRP Levels With Infectious Status

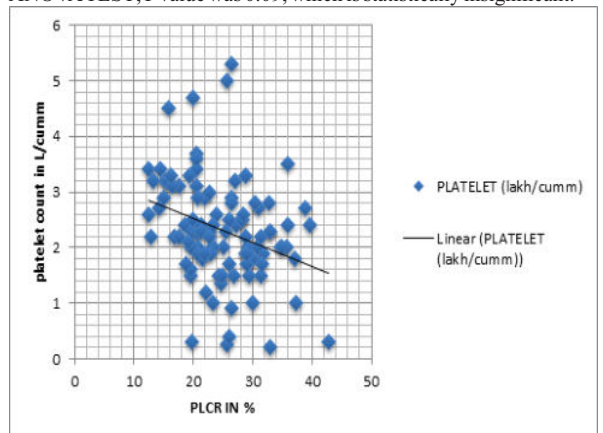
Out of 100 cases studied 10% had positivity for CRP out of which 12% were culture positive cases. The statistical test used was ANOVA TEST; P value is 0.26, which is statistically insignificant, suggesting no significant co relation.

Platelet Count Variation With PDW Variation

Table 2. Platelet Count Variation With PDW Variation

	PDW (<9fl)	PDW(9 to14fl)	PDW(>14fl)
SEVERE THROMBOCYTOPENI A (<0.5L/CUMM)		3	2
MODERATE THROMBOCYTOPENI A (1.0L TO 0.5L/CUMM)		2	2
MILD THROMBOCYTOPENI A (1.5L TO 1.0 L/CUMM)		6	2
NORMAL PLATELET COUNT (1.5L TO 4.5L/CUMM)	4	68	8
THROMBOCYTOSIS(> 4.5L/CUMM)		3	

PDW was studied in relation with platelet count. Platelet count was found to be inversely related to PDW. The statistical test used was ANOVA TEST; P value was 0.09, which is statistically insignificant.



thrombocytopenia. P-LCR & PDW was decreased in patients with thrombocytosis than in normal while it was increased in thrombocytopenia.

Severe degree of thrombocytopenia was seen in 29.4% of sepsis proven cases. PLCR increased with gestational age, which was significant.

Babu E et al [21] found that in patients with high counts, P-LCR was significantly decreased in reactive thrombocytosis than neoplastic thrombocytosis. P-LCR was increased with hypo proliferative thrombocytopenia though it was not statistically significant. P-LCR was inversely related to platelet count and directly related to PDW and MPV.

Torkaman M et al [22], reported that Enterobacter species is the commonest organism causing neonatal sepsis accompanying thrombocytopenia. In our study klebsiella pneumonia was the commonest organism causing neonatal sepsis accompanying thrombocytopenia.

Bonifacio L et al [23], reported that majority of thrombocytopenia (67%) was diagnosed after 72 hours of age. In our study majority of thrombocytopenia (52.3%) was diagnosed after 72 hours of age.

Thrombocytopenia is also known to be of prognostic value. Thrombocytopenia was found to be consistently associated with poor prognosis, confirming the finding of other studies.

Guida JD et al sepsis is frequently associated with thrombocytopenia and an elevation in MPV. However, fungal and Gram-negative pathogens are associated with a lower platelet count and more prolonged thrombocytopenia compared with Gram-positive pathogens.

Scheifele et al [24] demonstrated evidence of a relationship between Gram-negative infections and thrombocytopenia. In our study 52.3% of thrombocytopenia was seen in Gram-negative infections. The majority of Gram-Positive organisms isolated were CONS. Klebsiella pneumonia and pseudomonas aeruginosa were the most common Gram-negative organisms isolated. The most common fungal isolates was candida albicans. Similar findings were seen in our study.

Jyoti et al [25] found that Platelet distribution width (PDW) is an indicator of variation in platelet size, which may be a sign of active platelet release. Platelet large cell ratio can be a good aid in the differential diagnosis of conditions associated with abnormal platelet counts.

MPV along with PDW, Pct and P-LCR is predictive of many disease conditions. MPV seems to be increased when there is destruction to platelets. This condition is observed in immune thrombocytopenic purpura (ITP), myeloproliferative diseases and Bernard-Soulier syndrome [25]. As these indices vary with bone marrow response & immune mediated destruction can be used in differentiating hypo productive & hyper destructive thrombocytopenia. Sepsis is associated with both decreased marrow response & immune mediated destruction (DIC). Increased level of MPV and normal platelet count is observed in patients with heterozygous thalassemia or iron deficiency anemia.

Ossler JC [26] found that PDW expresses the distribution of the size of platelets produced by the megakaryocyte. In cases of autonomous platelet hyper production, one could expect a diminished control by the megakaryocyte of the platelet size, reflected by a widened dispersion.

LIMITATIONS OF THE STUDY

Time taken from collection of the sample & processing can cause variation in the values slightly. The sample size is less for any conclusive result. Positivity of CRP was very less in our study, may be because of time of sampling & cut off value of CRP is higher compared to other studies. Serial values of platelet & platelet indices must be studied for very good correlation.

CONCLUSION

Septic patients with Gram-negative organisms or fungi had a higher incidence of thrombocytopenia when compared with Gram-positive patients. Thrombocytopenia was seen more with late onset sepsis than early onset sepsis. Platelet indices values (PDW & PLCR) were

inversely related to the platelet count. As these indices vary with bone marrow response & immune mediated destruction can be used in differentiating hypo productive & hyper destructive thrombocytopenia. Since CRP & blood culture take 1 to 2 days to be positive, Indices can be used on day 1 for early screening & prompt treatment. The advantage of studying the hematological profile of neonates suspicious of having sepsis is that these tests can be done rapidly even in small hospitals, allowing prompt treatment to neonates with sepsis and minimizing therapy to those without infection. Hence, correlation of both clinical and laboratory data are necessary in neonatal sepsis.

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Platelet Count Variation With PLCR Variation

PLCR was studied in relation with platelet count. Platelet count was found to be inversely related to PLPCR. The statistical test used was ANOVA TEST; P value was 0.29, which is statistically insignificant.

DISCUSSION

The gold standard for diagnosis of neonatal sepsis is a positive blood culture, which requires a minimum period of 48-72 hours and yields positive results in 25-70% of cases [3]. About 10% to 60% of newborns with proven bacterial invasion of the bloodstream or meninges have platelet counts of less than 100,000/mm³ [3]. Average duration of thrombocytopenia is about 1 week but can be as long as 2 to 3 weeks [4,5].

Incidence of sepsis

Of the 100 neonates evaluated 42% showed positive blood culture. Ghosh et al. had 28.5% culture positive cases. Kumar et al. found blood culture positivity in 42% cases. More than 25% of the cases were microbiologically positive for sepsis in the study by Joshi et al [3].

Age And Sex Incidence

The age of the neonates ranged from newborns to 28 days old. Of the 100 neonates in the study, 69 were males and 31 were females. In the sepsis proven group 57% of the infants were males. Male infants are 2-6 times more likely to develop perinatal sepsis than females as reported in several studies.

Gestational Age

64% of infants with confirmed sepsis were preterm. In the preterm neonates, the inherent deficiencies are common in immune system, hence the risk of sepsis is increased, as seen in several studies [6,7]

Onset Of Symptoms

67% of the neonates in the study presented with early onset type of sepsis. This is similar to the study conducted by Rodwell et al [8]. and Tallur et al [9]. In the present study 33% of the neonates had Late onset sepsis.

Among the culture positive pseudomonas is predominant bacteria seen in 50% of cases, klebsiella seen in 28.5%, CONS in 16.7% & candida in 4.76%. Culture positivity is seen more in early onset sepsis than late onset sepsis. Early onset sepsis was seen in 67% & 33% late onset sepsis. Gram-negative infections were seen more common in both early & late onset sepsis. 58% of EOS were pseudomonas, 25% were klebsiella & 18% were CONS.

In West BA and Peterside O [10] study Klebsiella pneumonia (65.4%) and Staphylococcus aureus (15.4%) were the commonest organisms isolated in neonates with EOS while the least were Pseudomonas aeruginosa (2.6%) and Enterococcus faecalis (2.6%). In late onset sepsis 35% of cases were Klebsiella & Pseudomonas, 15% percent of cases were CONS & Candida.

CLINICAL PRESENTATION

Bortolussi et al [11]. have discussed the difficulty in differentiating early neonatal sepsis from Hyaline membrane disease (HMD) during initial phase of the disease.

Early onset sepsis usually presents within 72 hours of life. In severe cases, the neonate may be symptomatic in utero (fetal tachycardia, poor beat to beat variability) or within few hours after birth.

MATERNAL RISK FACTORS AND PERINATAL COMPLICATIONS

Caesarean section was seen in 66% of the cases with sepsis, In Thomas et al study 38% cases of proven sepsis were born by cesarean section.

Meconium stained amniotic fluid was seen in 10% of cases as a perinatal risk factor. Kuruvilla et al found meconium stained amniotic fluid in 14% of the cases.

PROM was seen in 12.5% of neonates with septicemia. In a study, St.Geme et al. have concluded that incidence of documented sepsis in neonates born to mothers with rupture of membranes for more than 24 hours is about 1% [12].

Kuruvilla et al [13] observed a 4-11 fold increase in the risk of infection when either amnionitis, male gender or prematurity were added to the primary risk factors of PROM.

Speer et al. [14] found that gestational age less than 34 weeks and ruptured membranes of more than 24 hours in association with infected amniotic fluid places the newborn at a 1-5% chance of acquiring infection.

Bada et al [15]. reported a four fold increase in amnionitis when associated with PROM.

BLOOD CULTURE RESULTS-ORGANISMS ISOLATED

Table 3

	Chandra et al. 1988	Krishna et al. 2000	Ghosh et al 2001	Kumhar et al. 2002	Present study 2012
Klebsiella pneumonia	20.8	37.9	17	33.8	28.5%
Escherichia coli	37.5	20.6	30	4.6	
Coagulase negative Staphylococci	-	-	-	7.9	16.7%
Pseudomonas aeruginosa	12.5	10.3	13.3	10.2	50%
Non fermenting gram negative bacilli	-	3.4	-	-	
Enterococci	-	-	3.3	7.5	
Staphylococcus aureus	28.2	27.5	27	24.4	
Alcaligenes faecalis	-	-	-	4.9	
Group B Streptococci	-	-	6.7	-	
Candida					4.7%

The commonest pathogen isolated in the blood culture in the present study was pseudomonas aeruginosa followed by klebsiella. In the study conducted by Krishna et al. and Kumhar et al. Klebsiella was the commonest organism identified.

In contrast to the developed world where Group-B Streptococcus (GBS) continues to be the most common bacterial pathogen, studies from developing countries have identified Gram-negative organisms as more frequently infecting agents. Group B Streptococcus (GBS) and Escherichia coli account for about 60% of cases in North America and Europe.

C-Reactive Protein

C-Reactive protein of >6 mg/l was considered as raised [16]. C Reactive protein levels were raised in 12% of neonates with sepsis and 15% of the neonates with probable sepsis. 3% of the neonates who were non infected showed an elevated C-Reactive protein level.

Many authors have used CRP levels along with various hematological parameters like WBC count, polymorph nuclear count and band cell count to achieve high sensitivity and specificity [17,18,19]

In diagnosis of early-onset sepsis, previous studies reported on widely differing sensitivities and specificities of CRP ranging from 29 to 100% and from 6 to 100%, respectively [16].

A poor response is particularly frequent among infants whose infection occurs during the first 12 to 24 hours of life and among infants with infection caused by gram-positive bacteria, including group B streptococci [20] Serial measurement of c-reactive protein is used. But the sensitivity and specificity vary widely in different studies. Timing of sample is important, because it can be delayed for several hours after the onset of illness and CRP is elevated in other inflammatory conditions of tissue injury.

PLATELET COUNT AND PLATELET INDICES:

Incidence of thrombocytopenia among NICU admitted cases is 22% to 35% Guida JD [20] study showed sepsis in 16% patients in the study population. Of the sepsis neonates, 54% were associated with thrombocytopenia and 61% with an elevation in MPV.

In our study thrombocytopenia was seen in 17% of cases. 24% of sepsis proven cases had thrombocytopenia & 29 % of probable sepsis had