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EVALUATION OF PLATELET AND ITS INDICES AS A DIAGNOSTIC TOOL IN NEONATAL SEPSIS – A HOSPITAL BASED CASE-CONTROL STUDY

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Corresponding Author:
Dr Aukifa khamim Sabibahul Islam
Email: aukifa.islam.yahoo.co.in

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Aukifa Khamim Sabibahul Islam[1], Bhanu Priya Pegu[2], Rita Panyang Kataki[3]

[1]Associate Professor, Department of Pediatrics, Assam Medical College and Hospital. Dibrugarh, India
[2]Senior Resident, Pediatrics, Pratiksha Hospital, Guwahati, India
[3]Associate Professor, Department of Pediatrics, Tinsukia Medical College and Hospital. Tinsukia, India.

Abstract

Background: Neonatal sepsis is a common cause of neonatal morbidity and mortality in developing countries. It is a diagnostic challenge as there are overlapping signs and symptoms which preclude a specific diagnosis of sepsis. Thrombocytopenia is often found among the sick neonates of the neonatal intensive care unit (NICU) and there have been studies showing significant changes in platelet indices in patients with neonatal sepsis. This study was carried out to determine the relationship between neonatal sepsis and platelet indices [platelet count, mean platelet volume (MPV), and platelet distribution width (PDW)] in a Newborn unit of a tertiary care hospital of upper Assam. **Materials and Methods:** The study was conducted on 180 neonates in the Neonatal Intensive Care Unit (NICU). 90 neonates with clinical, probable, and culture-proven sepsis were taken as cases and 90 gestational age and weight-matched neonates without any suspicion for sepsis were taken as control. Statistical analysis of data was performed using Statistical package for social sciences, version 20.0 and Microsoft excel 2010. **Result:** The babies in cases group had a greater number of subjects with higher platelet indices than the control group. 76.67% of cases and 23.33% of controls had thrombocytopenia. Culture proven sepsis had the most severe degree of thrombocytopenia. Except for Platelet Distribution Width, platelet indices did not vary significantly with the onset of sepsis. **Conclusion:** In this study it is found that thrombocytopenia, high Platelet Distribution Width and high Mean Platelet Volume are associated with neonatal sepsis. So platelet indices can serve as a diagnostic marker for neonatal sepsis and can be combined with the existing sepsis screen.

INTRODUCTION

Neonatal sepsis is a common cause of neonatal morbidity and mortality in developing countries. It is a diagnostic challenge as there are overlapping signs and symptoms which preclude a specific diagnosis of sepsis.

Neonates are fragile and can deteriorate rapidly, so rapid diagnosis and prompt management is required. Blood culture is the gold standard for diagnosis of neonatal sepsis.[1] But it has been found that, in the clinically suspected early onset neonatal sepsis (EONS) and late onset neonatal sepsis (LONS), only 20% and 30% have a positive blood culture respectively.[2] Sepsis screening too has a variable sensitivity and specificity.[3] The limitations of blood culture, its low positivity rates, and poor diagnostic capability of sepsis screen in neonates make the diagnosis of sepsis difficult, and thus the need for better diagnostic parameters arises.[4]

Thrombocytopenia is often found among the sick neonates of the neonatal intensive care unit (NICU) and there have been studies showing significant changes in platelet indices in patients with neonatal sepsis. The autoanalyzers now-a-days readily provide platelet indices along with platelet counts without any additional cost. However, these indices are not given proper weightage often. The important platelet indices available for clinical utility include mean platelet volume (MPV), platelet distribution width (PDW) and plateletcrit that are related to morphology and proliferation kinetics of platelets.[5]

The pathogenesis is not completely understood but it has been suggested that bacteria or bacterial products may cause endothelial damage leading to platelet adhesion and aggregation or may bind directly to platelets leading to aggregation and accelerated

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clearance from circulation.[6,7] So, haematological finding like platelet indices which includes plateletcrit (=MPV × platelet count), PDW (Platelet Distribution Width) and MPV (Mean Platelet Volume) can be helpful as an additional diagnostic tool in early diagnosis of neonatal sepsis.[8] It has been seen that platelet count decreases and MVP and PDW increases in neonatal sepsis.[9]

Despite being a promising and convenient marker for sepsis, there have been only a few studies on the utility of platelet markers in neonatal sepsis. There are not many studies on this topic from our region. None of the available studies compares platelet indices with the existing sepsis screen in prediction of neonatal septicemia. So, looking at the paucity of studies in this issue, the present study is an effort to fulfil the gap in the existing literature and would evaluate the significance of platelet indices either alone or in combination with existing sepsis screen as a marker of neonatal sepsis.[10]

This study was undertaken to find out if there is any association between platelet indices and neonatal sepsis and to enhance our ability to diagnose neonatal sepsis early.

MATERIALS AND METHODS

This was a hospital-based Case Control Study done in the Neonatal Intensive Care Unit (NICU), of a tertiary care teaching hospital in northeast India for a duration of 1 year, from July 2020 to June 2021. The study was undertaken after clearance by the Institutional Ethics Committee with certificate number AMC/EC/PG/8909/2020-2021. Informed and written consent was taken from the parents/guardian after explaining properly about the study.

Inclusion criteria

For Case, Inborn neonates with clinical sepsis, probable sepsis and culture proven sepsis were included in the study. For control - A newborn without any evidence of sepsis was taken as control.

Exclusion criteria

Neonates with congenital or acquired cause of thrombocytopenia, mother who had history of Immune-Thrombocytopenic Purpura or Systemic Lupus Erythromatosis and neonates who received antibiotics for more than 48 hrs.

Sample size: Considering 95% confidence interval with margin of error 5% and referring the findings of a study by Mittal et al, 2020, sample size was calculated and rounded off to 180.[8] Out of which 90 were taken as cases and 90 were taken as control.

Data collection: After enrolment of the case, a detailed history and clinical examination of the neonate was performed. The findings were recorded in the predesigned proforma. For every case of suspected sepsis or culture proven sepsis, a newborn without any evidence of sepsis was taken as control (gestational age was taken as match). In all the neonates, maternal details regarding her pregnancy, medical and obstetrical problems was recorded in a predesigned proforma. The data were entered in excel spread sheet.

Sample collection and laboratory analysis: All babies enrolled were investigated for blood culture, sepsis screen---C reactive protein (CRP), total leukocyte count (TLC), absolute neutrophil count (ANC), immature to total neutrophil (IT) ratio, µESR, hemoglobin value and platelet indices (platelet count, MPV, PDW). For this, approximately 2 mL of venous blood was drawn from each neonate through peripheral veins. The samples were sent to Pathology and Microbiology laboratory for investigations. Based on the reports of blood culture and sepsis screen, the neonates were classified into culture proven sepsis, probable sepsis with negative blood culture, clinical sepsis with negative sepsis screen and blood culture and no sepsis on the basis of definitions provided by the CDC. Blood culture was collected from a peripheral vein under aseptic precaution before starting antibiotics. Full blood count was performed using the Sysmex - XN - 550, a six- part auto analyzer able to run 44 parameters per sample including hemoglobin concentration, packed cell volume, mean corpuscular hemoglobin, mean cell volume, mean corpuscular hemoglobin concentration, white blood cells, platelet count and mean platelet volume, platelet distribution width and other platelet indices, reticulocyte count and also body fluids.

Sepsis Screen Criteria[11]

Presence of any two of the following was considered as positive sepsis screen

1. ANC< 1800cells/mm3
2. I/T ratio >0.2
3. ANC were plotted on Monroe's chart for preterm neonates and Mouzinho's chart for term neonates [12,13]
4. C-Reactive Protein (CRP) >1mg/L.
5. µESR value (in mm in first hour) >3+age in days in the first week of life - or >10 thereafter was considered positive.

Thrombocytopenia and Grading: Platelet count < 1,50000/mm3 was considered as thrombocytopenia

Grading: Severity of thrombocytopenia was graded as follows,[14]

Mild thrombocytopenia: Platelet count 1,00000 to < 150000 cells/mm3

Moderate thrombocytopenia: Platelet count 50000 to 99000 cells/mm3

Severe thrombocytopenia: Platelet count <50000 cells/mm3

Mean Platelet Volume: It is a machine-calculated measurement of the average size of platelets found in blood.

Platelet Distribution Width: It is a measurement of platelet anisocytosis calculated from the distribution of individual platelet volume.

Plateletcrit: Mean platelet volume × platelet count

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Statistical analysis: The statistical analysis of data was performed using the computer program, Statistical Package for Social Sciences (SPSS for windows, version 20.0 Chicago, SPSS Inc) and Microsoft excel 2010. Results on continuous variables were presented as mean ± standard deviation. Discrete data were expressed as numbers (%) and were analysed using Chi-square test, Fischer's Exact test and Student's t-test. A p-value of less than 0.05 was considered as statistically significant.

RESULTS

The study was conducted on 180 neonates, out of which 90 neonates with suspected and clinical sepsis were taken as cases, and 90 neonates without any suspicion of sepsis were taken as controls. The babies in cases group had a greater number of subjects with higher platelet indices than the control group (P < 0.05). [Table 1]

In our study, of the total 90 cases, 57 (63.33%) had probable sepsis, 23 (25.55%) had culture proven sepsis and 10(11.11%) had clinical sepsis. [Table 2)]. Out of the 90 cases 69 (76.67%) neonates had thrombocytopenia, of which, 44(63.7%) had mild, 20 (28.98%) had moderate and 5 (7.24%) had severe thrombocytopenia.

Among the 69 neonates with thrombocytopenia 45(78%) had probable sepsis, 18(78%) had culture proven sepsis and 6(60%) cases had clinical sepsis. Out of 45 probable sepsis 24 (53.3%) showed mild thrombocytopenia, 18 (40%) showed moderate and 3(6.6%) showed severe thrombocytopenia. Out of 23 culture proven sepsis, 16 (88.88%) showed mild, 2 (11.1%) showed severe degree of thrombocytopenia. Among the 6 clinical sepsis cases, 4 (66.6%) had mild, 2(33.3) had moderate whereas none showed severe degree of thrombocytopenia.

Out of 21 controls with thrombocytopenia, 14 (66.6 %) showed mild thrombocytopenia, 7 (33.3%) showed moderate thrombocytopenia whereas no severe thrombocytopenia was seen in our study. 42 (73.6%) of probable sepsis cases, 19(82.6%) of proven sepsis and 6(60%) of clinical sepsis cases were having MPV >11 fl. 38(66.6%) of probable sepsis cases, 17(73%) of proven sepsis cases and 5 (50%) of clinical sepsis cases were having PDW >14 fl. [Table 3] It had been found that among the 67(74.4%) cases with increased MPV (>11 fl), 57 cases (85%) had thrombocytopenia and among 60 (66.67%) cases with increased PD (>14 fl), 55 cases (91.6%) had thrombocytopenia.

Here it was observed that the mean platelet count was 1.31 ± 0.75 lacs/mm3 in cases and 2.29 ± 0.89 lacs/mm3 in controls group, being significantly less in the case group than in control group, (p<0.001). The mean MPV value was 12.86 ± 2.69 fl in cases and 10.57 ± 1.31 fl in controls, significantly more in the case group than in control group, (p<0.001). The mean PDW value was 17.30 ± 12.05 fl in cases and 13.20 ±1.75 fl in controls, significantly more in the case group than in control group, (p<0.0017).

In our study 51(73.9%) neonates with EONS and 18(85.7%) neonates with LONS had a platelet count <1.5 lacs/mm3 with difference being statistically insignificant (p=0.2418). Similarly, 49(71%) neonates with age less than 72 hours and 18(85.7%) neonates more than 72 hours age group were having MPV >11 fl, with difference being statistically insignificant, (p=0.1762). Again, 41(59%) neonates with age less than 72 hours and 19(90.4%) neonates more than 72 hours age group were having PDW >14 fl, with difference being statistically significant, (p=0.00821). [Table 4]

Table 1: Platelet indices in Cases and Controls.

Platelets Indices	Cases (n=90)		Controls (n=90)		p-value*
	n	%	n	%	
Platelet Count (lacs/mm3)					<0.001
< 1.5	69	76.67	21	23.33	
≥ 1.5	21	23.33	69	76.67	
MPV (fl):					<0.001
>11	67	74.44	24	26.67	
6.5-11	23	25.56	66	73.33	
≤ 6.5	0	0.00	0	0.00	
PDW (fl):					<0.001
>14	60	66.67	32	35.56	
≤ 14	30	33.33	58	64.44	

Table 2: Degree of Thrombocytopenia in Cases and Controls

Degree of thrombo-cytopenia	Cases						Total Thrombo-cytopenia	Controls	
	Probable Sepsis (n=57)		Proven Sepsis (n=23)		Clinical Sepsis (n=10)				
	n	%	N	%	n	%	N	N	%
Mild	24	53.3	16	88.8	4	66.6	44	14	66.6
Moderate	18	40	0	0	2	33.3	20	7	33.3
Severe	3	6.6	2	11.1	0	0	5	0	0
TOTAL	45 (78%)	100	18 (78%)	100	6 (60%)	100	69 (76.67%)	21 (23%)	100

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Table 3: Platelet Indices in Different Groups of Cases

Parameter	Cases						Total	
	Probable Sepsis		Proven Sepsis		Clinical Sepsis		n=90	%
	n=57	%	n=23	%	n=10	%		
Platelet Count (< 1.5 lacs/mm3)	45	78	18	78	6	60	69	76.67
MPV (> 11 fl)	42	73.6	19	82.6	6	60	67	74.44
PDW (> 14 fl)	38	66.6	17	73	5	50	60	66.67

Table 4: Comparisons of Platelet Indices in EONS and LONS in Cases

Platelets indices	Eons		Lons		p-value*
	n=69	76.66%	n=21	23.33%	
Platelet Count (< 1.5 lacs/mm3)	51	73.9	18	85.7	0.2418
MPV (> 11 fl)	49	71	18	85.7	0.1762
PDW (> 14 fl)	41	59	19	90.4	.00821#

DISCUSSION

Incidence of neonatal sepsis or bacteremia in asymptomatic infant is low, but not negligible.[15,16] This study was conducted in 90 control and 90 case , out of the total 90 sepsis cases, 76.67% of neonates had thrombocytopenia, out of which, 63.77% had mild, 28.98% had moderate and 7.24% had severe thrombocytopenia. The prevalence of thrombocytopenia in sepsis is variable and different values have been reported by workers across the globe. Alshorman A et al. in their study showed that 42.8% babies with sepsis developed thrombocytopenia.[17] In another study by Ahmad I et al, it was seen that prevalence of thrombocytopenia was 24.7% in neonatal sepsis.[18] Choudhary RR found that 81.12% of cases of neonatal sepsis developed thrombocytopenia.[19] In the study by Mittal et al, 80.9% of cases of neonatal sepsis developed thrombocytopenia.[8] This variation may be attributed to the fact that in this study we considered a cut off of platelet counts of less than 1.5 lakhs/mm3 and other contemporary studies considered a cut off of 1 lakhs/mm3.

In our study MPV in cases and controls differed significantly between the two groups (P<0.001). An increase in MPV was found more frequently in cases than in controls. MPV was found to be increased in 74.44 % of cases in neonatal sepsis which was far greater when compared with the results of study by Alshorman A et al which shows 27.8% increase in MPV in all cases of sepsis.[17]

In a similar study by Choudhary RR, they found that MPV in cases and controls differed significantly between the two groups.[18] It showed that an increase in MPV was found more frequently in cases than in controls. It was found to be increased in 70.7% of case. Patrick RH et al also found that MPV was increased more in cases with late-onset sepsis.[20]

Our study shows that PDW was increased significantly in the cases group as compared to control group (p<0.001). PDW was increased in 66.67 % of cases in neonatal sepsis which was far greater when compared with the study by Abdalla et al which shows that PDW increased in 38% cases of sepsis. It is comparable with the study by Mittal et al where PDW was found to be increased in 67% cases (n = 188).[8] Choudhury RR also found that PDW was increased in 38% cases of sepsis.

In our study the two groups were significantly different when mean of platelet indices were compared. It was observed that the mean platelet count was 1.31 ± 0.75 lacs/mm3 in cases and 2.29 ± 0.89 lacs/mm3 in controls group, being significantly less in case group than in control group, (p<0.001). The mean MPV value was 12.86 ± 2.69 fl in cases and 10.57 ± 1.31 fl in controls, significantly more in case group than in control group, (p<0.001). The mean PDW value was 17.30 ± 12.05 fl in cases and 13.20 ±1.75 fl in controls, significantly more in case group than in control group, (p=0.0017).

Similar finding was seen in the study by Choudhary RR et al. It was observed that the mean platelet count was 1.07 ± 0.698 lacs/mm3 in cases and 2.04 ± 0.759 lacs/mm3 in controls group, being significantly less in case group than in control group, (p<0.0001). The mean MPV value was 11.82 ± 1.69 fl in cases and 9.75± 1.45 fl was in controls, significantly more in case group than in control group, (p<0.0001). The mean PDW value was 20.62 ± 2.22 fl in cases and 18.64±1.96 fl was in controls, significantly more in case group than in control group, (p<0.0001).[15]

In our study changes in platelet indices were seen more in neonates with age more than 72 hours. Among the neonates whose age was more than 72 hrs, 85.7% neonates had thrombocytopenia, 85.7% had MPV >11 fl and 90.4% neonates had PDW >14 fl. Hence alteration in platelet indices was seen more in LONS.

When we compared platelet indices in babies with EONS and LONS in the study by Mittal et al it was seen that prevalence of thrombocytopenia was significantly higher in LONS. He also found a significantly higher MPV in the LONS group.[8]

Limitation of study: As the study was conducted in a single hospital, the sample size is less in number and it might not represent the overall finding. Follow-up was not done to find out if the platelet indices are related to outcome of the sepsis babies.

CONCLUSION

The platelet count decreased with the development of sepsis and PDW and MPV increased in babies with

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sepsis. There was severe degree of thrombocytopenia in culture proven neonatal sepsis cases. Platelet indices as a whole did not differ significantly with onset of sepsis. It was concluded from this study that platelet indices may serve as an important tool to aid sepsis screening and they may be combined with the existing sepsis screen to diagnose neonatal sepsis.

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