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Original Article

Paediatrics Section

Diagnostic Accuracy of Platelet Indices as a Marker for Sepsis in Neonates: A Case-control Study

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ABSTRACT

Introduction: Diagnosis of sepsis in neonates is challenging due to overlapping of signs and symptoms. Currently blood culture and sepsis screen are used for diagnosis. Blood culture is the gold standard but its usefulness is limited due to low positivity, delay in reporting. Sepsis screen has variable sensitivity and specificity. To overcome these limitations, platelet indices can be used in diagnosis.

Aim: To assess platelet indices as a marker to diagnose neonatal sepsis and to calculate sensitivity and specificity of platelet indices in comparison to clinical symptoms, sepsis screen and blood culture.

Materials and Methods: This case-control study was conducted from June 2021 to November 2021 in Neonatal Intensive Care Unit (NICU) of tertiary care centre, Karnataka, India. Total of 198 neonates with signs and symptoms of sepsis and/or risk factors of sepsis were included. Weight and gestational age matched 198 healthy neonates served as control. Investigations include blood culture, sepsis screen and platelet indices were sent. Platelet indices were compared between cases and controls. Sensitivity and specificity of platelet indices were calculated in culture positive, screen positive and both negative groups. Data of both the groups were compared using Independent t-test and Chi-square test.

Results: Demographic profile was homogenous between both study groups. Out of 198 cases, 145 (73.2%) had platelet count <1.5 lakhs, 132 (66.7%) had Mean Platelet Volume (MPV) >10.8 fl and 109 (55.05%) had Platelet Distribution Width (PDW) >19.1 fl. These values were statistically significant (p-value<0.001) when compared with controls. Statistically significant (p-value <0.001) difference was seen in mean of platelet count (1.3±0.7 lakhs/cumm), MPV (10.7±0.8 fl), PDW (19.1±2.3 fl) and Plateletcrit (PCT) (0.1±0.1) between cases and controls. Platelet count was more sensitive (73.2%) and specific (81.3%) marker when compared between cases and controls.

Conclusion: Platelet indices are cheaper and widely available markers in diagnosing neonatal sepsis. Thrombocytopenia, high MPV and high PDW were associated with neonatal sepsis.

Keywords: Mean platelet volume, Neonatal sepsis, Plateletcrit, Platelet count, Platelet distribution width

INTRODUCTION

Sepsis is a clinical syndrome characterised by signs and symptoms of infection with or without bacteremia. It is the most common cause of mortality in neonates. It includes septicemia, meningitis, pneumonia, arthritis, osteomyelitis and urinary tract infection. It can be early onset (<72hrs) or late onset (>72 hrs). It is more commonly in preterm and low birth weight babies [1].

Even though there is improvement in management, but there are many challenges in diagnosing sepsis. It is estimated that 20% of neonates develop sepsis and 1% deaths are related to sepsis [2]. Diagnosis of sepsis in neonates is challenging due to overlapping of signs and symptoms. Blood culture and sepsis screen are used to diagnose sepsis. Currently blood culture is the gold standard test to diagnose neonatal sepsis, but its usefulness is limited due to low positivity and delay in reporting. Around 50% of Early Onset Sepsis (EOS) and 40% of Late Onset Sepsis (LOS) has blood culture positive [3]. Sepsis screen has variable sensitivity and specificity ranging from 50-90% [4].

To overcome these limitations, platelet indices like platelet count, Mean Platelet Volume (MPV), Platelet Distribution Width (PDW) and Plateletcrit (PCT) can be used in diagnosis. Platelet indices are easily available while obtaining Complete Blood Count (CBC) by autoanalysers. There are few studies in adults in diagnosing sepsis [5,6]. But only few studies [7-10] are there to demonstrate usefulness of platelet indices in diagnosing sepsis in neonates. Hence, present study was conducted to assess usefulness of platelet indices in diagnosing neonatal sepsis and to assess difference in platelet indices with respect to clinical symptoms, sepsis screen and blood culture.

MATERIALS AND METHODS

This case-control study was conducted over a period of 6 months from June 2021 to November 2021 in NICU of Department of Paediatrics in a tertiary care centre, Karnataka, India. The study was approved by Institutional Ethical Committee [IEC no. SIMS/IEC/441].

Inclusion criteria: All neonates admitted to NICU during study period with signs and symptoms of sepsis and/or neonates born to mothers with risk factors of sepsis like fever, foul smelling discharge, uterine tenderness, leaking per vagina >24hrs, were taken as cases. For each case, weight and gestational age matched healthy neonate were taken as control.

Exclusion criteria: Congenital or acquired causes of thrombocytopenia other than sepsis i.e., intrauterine growth restriction, perinatal asphyxia, maternal antiplatelet drug usage, autoimmune thrombocytopenia, alloimmune thrombocytopenia were excluded from the study.

Sample size calculation: Sample size was calculated based on expected sensitivity of 85%, absolute precision of 5% at 95%

significance level and 195 cases were required. Sample size was calculated using OpenEpi software (version 3.1) [11].

Parameters Assessed

Sign and symptoms of sepsis includes core body temperature of >38.5°C or <36°C, cardiovascular instability- bradycardia or tachycardia, reduced urine output (<0.5 mL/kg/hr), hypotension (<5th centile for gestational age), mottled skin, impaired peripheral circulation, petechial rashes, sclerema, apnoea, tachypnoea (>60 breaths/min), feeding intolerance, poor sucking, abdominal distension, irritability, lethargy and hypotonia [12].

Blood investigations including blood culture, sepsis screen and platelet indices were sent for testing before starting antibiotics. Under aseptic precaution 1 mL of venous blood was sent for culture and observed at least after 72 hrs for any growth.

Sepsis screen include total leucocyte count (TLC- <5000/cumm), Absolute neutrophil count (ANC<1800/cumm), C-reactive protein (CRP>10), Micro-Erythrocyte Sedimentation Rate (ESR) (>15mm in 1st hr) and Immature to total leucocyte ratio (I: T>0.2). At least 2 abnormal parameters were taken to define sepsis screen [13]. Platelet indices include platelet count, Platelet Distribution Width (PDW), Mean Platelet volume (MPV) and Plateletcrit (PCT) were sent and age appropriate cut-off were taken as given in [14,15] [Table/Fig-1].

Parameters	Cut-off
Platelet count	<150000/cumm
Platelet distribution width (PDW)	>19.1 fl
Mean platelet volume (MPV)	>10.8 fl
Plateletcrit	<0.1%

[Table/Fig-1]: Cut-off values for platelet indices [14,15].

Based on the reports, all the cases were classified into 3 groups:

- **Clinical sepsis:** It is defined as presence of atleast two clinical symptoms, but with neither laboratory signs nor positive blood culture.
- **Screen positive sepsis:** It is characterised by blood culture negative, but meeting the criteria of presence of at least two laboratory signs of sepsis screen, and
- **Culture positive sepsis:** It is characterised by positive blood culture with clinical and/or laboratory evidence of sepsis [16,17].

Sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of platelet indices were calculated in each group.

Based on onset of symptoms, cases were divided into early onset and late onset sepsis. Early onset sepsis and late onset sepsis are characterised by onset of symptoms within 72 hrs and after 72 hrs of life respectively. Difference in platelet indices between both the groups were assessed [2].

STATISTICAL ANALYSIS

Data were entered into Microsoft Excel and statistical analysis was carried out in Statistical Package for the Social Sciences (SPSS) version 17.0 software. Qualitative variables were presented as frequency and percentages. Quantitative variables were presented as mean (standard deviation) or median (range) depending upon the distribution of data. Continuous variables like birth weight, gestational age and age of onset were compared between cases and controls using Independent t-test. Categorical variables were compared between the groups using Chi-square test. A p-value of less than 0.05 was considered as statistically significant.

RESULTS

Demographic details of cases with respect to birth weight, gestational age and gender were homogenous with control group (p-value>0.05). Mean of birth weight in cases and controls were 2.3±0.6 kgs and 2.4±0.8 kgs respectively with p-value of 0.16. Mean of gestational age in cases and controls were 36.5±2.8 weeks and 36.8±2.8 weeks respectively with p-value of 0.275. Male to female ratio in cases and controls were 1.1:1 and 1.17:1 respectively with p-value of 0.687.

Out of 198 cases, 84 were culture positive, 119 cases were screen positive and 52 had symptoms of clinical sepsis. There was overlapping of cases, as few culture positive cases also had screen positive. Out of 198 cases, 84 culture positive cases, 119 were screen positive (It included both culture positive and culture negative cases with sepsis screen postive) and 52 cases had both culture negative and screen negative status.

In this study, 145 (73.2%) cases had platelet count <1.5 lakhs/cumm, while only 37 (18.7%) controls had the same with significant p-value<0.001. Similarly, 132 (66.7%) cases and 41 (20.7%) controls had MPV >10.8 fl. This difference was statistically significant with p-value<0.001. Similarly, in cases group 109 (55.05%) neonates had PDW of >19.1fl, while in control group 45 (22.7%) neonates had the same with statistically significant difference (p-value<0.001). Similarly, in cases 67 (33.8%) neonates had PCT of <0.1%, while 3 (1.5%) neonates in control group had the same with statistically significant p-value<0.001 [Table/Fig-2].

Characteristics		Cases N (%)	Controls N (%)	p-value
Platelet count (lakhs/cumm)	<1.5	145 (73.2)	37 (18.7)	<0.001
	≥1.5	53 (26.8)	161 (81.3)	
MPV (fl)	>10.8	132 (66.7)	41 (20.7)	<0.001
	≤10.8	66 (33.3)	157 (79.3)	
PDW (fl)	>19.1	109 (55.05)	45 (22.7)	<0.001
	≤19.1	89 (44.9)	153 (77.3)	
PCT (%)	<0.1	67 (33.8)	3 (1.5)	<0.001
	≥0.1	131 (66.2)	195 (98.5)	

[Table/Fig-2]: Comparison of platelet indices between cases and controls.
MPV: Mean Platelet Volume; PDW: Platelet Distribution Width; PCT: Plateletcrit

It was observed that mean of platelet count in cases group was 1.3±0.7 lakhs/cumm while in control group was 2.3±0.9 lakhs/cumm, showing significantly (p-value <0.001) low in cases group compared to control group. Similarly, mean of MPV in cases was 10.7±0.8 fl while in control group was 9.7±1fl, showing significantly (p-value <0.001) high in case. The mean PDW of cases was 19.1±2.3 fl while for control group was 16.4±2.6 fl with significantly (p-value <0.001) high in cases. Similarly for plateletcrit, mean in cases was 0.1±0.1% and for controls was 0.2±0.1%, with significantly low in cases with p-value <0.001 [Table/Fig-3].

Characteristics	Cases Mean±SD	Controls Mean±SD	p-value
Platelet count (Lakhs/cumm)	1.3±0.7	2.3±0.9	<0.001
MPV (fl)	10.7±0.8	9.7±1	<0.001
PDW (fl)	19.1±2.3	16.4±2.6	<0.001
PCT (%)	0.1±0.1	0.2±0.1	<0.001

[Table/Fig-3]: Mean values of platelet indices between cases and controls.

In cases group, 65 (77.4%) culture positive cases, 93 (78.2%) screen positive cases and 31 (59.6%) clinical positive had platelet count of

less than 1.5 lakhs/cumm. Similarly, 60 (71.4%) culture positive cases, 81 (68.1%) screen positive cases and 32 (61.5%) clinical positive had MPV of >10.8 fl. 47 (56%) of culture positive cases, 67 (56.3%) screen positive cases and 29 (55.8%) of clinical positive had PDW of >19.1 fl.

In this study, platelet count was more sensitive (73.2%) and specific (81.3%) with respect to total cases when compared to other platelet indices. With respect to culture, platelet count was more sensitive (77.4%) and PDW was more specific (45.6%) [Table/Fig-4].

Diagnostic accuracy	Sensitivity	Specificity	PPV	NPV
All cases versus all controls				
Platelet count <1.5 laks/cumm	73.2	81.3	79.7	75.2
MPV>10.8fl	66.7	79.3	76.3	70.4
PDW>19.1fl	55.1	77.3	70.8	63.2
Screen positive vs screen negative in cases				
Platelet count <1.5 lakhs/ cumm	78.2	34.2	64.1	50.9
MPV>10.8fl	68.1	35.4	61.4	42.4
PDW>19.1fl	56.3	46.8	61.5	41.6
Culture positive vs culture negative in cases				
Platelet count <1.5 lakhs/ cumm	77.4	29.8	44.8	64.2
MPV>10.8fl	71.4	36.8	45.5	63.6
PDW>19.1fl	56.0	45.6	43.1	58.4

[Table/Fig-4]: Statistical parameters of platelet indices in different groups.
PPV: Positive predictive value; NPV: Negative predictive value

It was also observed that, there were 92 preterm and 106 term neonates. Out of them 52 (56.5%) preterm and 57 (53.8%) term neonates had platelet count <1.5 lakhs/cumm, but the difference is not statistically significant (p-value=0.698). Similarly 56 (60.9%) preterm and 76 (71.7%) of term neonates had MPV >10.8 fl, but difference is statistically not significant (p-value=0.107). Also 68 (73.9%) preterm and 77 (72.6%) term neonates had PDW>19.1, but difference is not statistically significant (p-value=0.840).

In cases group, 128 neonates had Early Onset Sepsis (EOS) and 70 neonates had Late Onset Sepsis (LOS). Out of them 96 (75%) neonates with EOS and 49 (70%) neonates with LOS had platelet count <1.5 lakhs/cumm. Similarly 84 (65.6%) neonates with EOS and 48 (68.6%) neonates with LOS had MPV >10.8 fl. 67 (52.3%) neonates with EOS and 42 (60%) of neonates with LOS had PDW>19.1. ALL these differences are not statistically significant with p-value >0.05 [Table/Fig-5].

	EOS (n=128)		LOS (n=70)		
Characteristics	n	%	n	%	p-value
Platelet count <1.5 lakhs/cumm	96	75.0	49	70.0	0.447
MPV>10.8fl	84	65.6	48	68.6	0.674
PDW>19.1fl	67	52.3	42	60.0	0.300

[Table/Fig-5]: Comparison of platelet indices between early and late onset symptoms.
EOS: Early Onset Sepsis; LOS: Late Onset Sepsis

DISCUSSION

In present study, low platelet count, high MPV and high PDW was seen more in cases than control with significant difference (p-value<0.001). In cases group, mean value of platelet count, MPV, PDW and plateletcrit were 1.3±0.7 lakhs/cumm, 10.7±0.8 fl, 19.1±2.3 fl and 0.1±0.1% respectively. Statistically significant (p-value<0.001) difference was noted in these values when compared with controls.

Neonatal sepsis remains the most common cause of mortality and morbidity despite advances in neonatal medicine, so early diagnosis and proper intervention is necessary to reduce mortality. No single test can reliably include or exclude neonatal sepsis. Currently, sepsis screen and blood culture are in use to diagnose sepsis. Even though blood culture is gold culture, its usefulness is limited by low positivity and delay in reporting. Sepsis screen has very low negative predictive value and also increases cost of investigation [7]. Platelet indices have gained interest in recent times for diagnosing sepsis in neonates. Platelet indices include platelet count, mean platelet volume, platelet distribution width and plateletcrit. These parameters are easily available while doing Complete Blood Count using autoanalyser [14].

This study had 198 cases. Out of them, 103 were males and 95 were females, which is the largest among the studies compared. Mean weight of study population is 2.3±0.6 kgs, mean gestational age is 36.5±2.8 weeks which was comparable with other studies [8,18]. Out of 198 cases, 106 were term and 92 were preterm neonates.

Study was classified as culture positive cases (84), screen positive cases (119) and both negative cases (52). Choudhary R et al., showed 69 cultures positive, 129 with screen positive cases and 41 both negative cases [7]. Similarly, Arya S et al., showed 65 culture positive sepsis and 123 culture negative cases [9]. Karne T K et al., showed 40 culture positive cases [10].

Thrombocytopenia is commonly seen in neonatal sepsis. Mechanism of thrombocytopenia is not clear but it was also observed that thrombocytopenia was associated with increased trombopoeitin [19]. Toll like receptors activates platelets to recognise bacteria in sepsis. Due to increased turnover of platelets leads to release of larger and younger platelets causes increase in mean platelet value. Platelet distribution width is also one of the platelet indices which is elevated in sepsis which ranges from 10-17.9% [20]. Plateletcrit is directly proportional to platelet count and MPV.

In this study, 145 cases had platelet count of <1.5 lakhs/cumm, 132 cases had MPV>10.8 fl and 109 cases had PDW of >19.1 fl, which was significantly more than control group with p-value <0.001. Similar findings were seen in Choudhary R et al., and Arya S et al., [7,9]. It was also observed that mean value of platelet count and plateletcrit was significantly lower than control group. Similarly, mean value of MPV and PDW significantly higher than control group with p-value <0.001. Similar findings were also seen in Choudhary R et al., Arya S et al., Bhakri A et al., [7,9,21].

There was no significant association found between platelet indices and gestational age. Similar finding was seen in Choudhary R et al., Anoop Bhakri et al., Choudhari DD et al., [7,8,21].

There was no significant difference in platelet indices between EOS and LOS. In contrary, Choudhary R et al., found that, platelet indices were altered more in LOS when compared to EOS with p-value <0.05 [7]. Arya S et al., showed significant difference in platelet count and MPV between EOS and LOS but no changes in PDW [9]. Choudhari DD et al., showed significant change in MPV between EOS and LOS [8].

In this study, when compared between cases and controls sensitivity of thrombocytopenia, MPV (>10.8 fl) and PDW (>19.1 fl) was 73.2%, 66.7% and 55.1% respectively, while the specificity was 81.3%, 79.3% and 77.3% respectively. When compared to blood culture, sensitivity of thrombocytopenia, MPV (>10.8 fl) and PDW (>19.1 fl) was 77.4%, 71.4% and 56% respectively, while the specificity is 29.8%, 36.8% and 56% respectively. If any of the platelet indices taken, sensitivity increases to 97.6%. Choudhary R et al., showed thrombocytopenia is most sensitive (83.7%) and specific (65%) marker. Arya S et al., showed thrombocytopenia is most sensitive (83.08%) marker and

PDW is most specific (35.77%) marker [7,9]. In contrary to the above studies, Rohadi A et al., showed platelet indices are more specific in diagnosing neonatal sepsis with less sensitivity [7,9,17] [Table/Fig-6].

Author name		Choudhary R et al., [7]	Rohadi A et al., [17]	Arya S et al., [9]	Present study
Place of study		Jodhpur, Rajasthan	Palembang, Indonesia	New Delhi, India	Shimoga, Karnataka
Year of study		2017	2019	2021	2021
Platelet <1.5 lakhs/cumm	Sensitivity	83.7	19	83.08	77.4
	Specificity	65	92.3	20.33	29.8
MPV >10.8 fl	Sensitivity	75.2	35.7	78.46	71.4
	Specificity	64.3	75.4	33.33	36.8
PDW >19.1 fl	Sensitivity	66.7	7.1	72.31	56
	Specificity	57.80	97	35.77	45.6
Any one positive	Sensitivity	-	84.1	63.08	97.6
	Specificity	-	65.5	46.34	7

[Table/Fig-6]: Comparison of statistical parameters of platelet indices in different studies [7,9,17].

Limitation(s)

The present study is a case-control study, hence follow-up of the neonates for change in platelet indices after starting treatment and after recovering from sepsis cannot be assessed. Other parameters like prematurity and type of organism may affect platelet indices but which was not defined in the study.

CONCLUSION(S)

This study showed platelet indices serves as a important tool in diagnosing neonatal sepsis. Thrombocytopenia is the most sensitive marker. Platelet indices have high sensitivity in diagnosing sepsis and sensitivity increases to 97% if any of platelet indices were taken but specificity of platelet indices was low. When platelet indices were combined with sepsis screen specificity can be increased. Further studies with larger sample size are necessary to strongly conclude this association. To conclude, platelet and its indices are cheaper and widely available markers in diagnosing neonatal sepsis in developing countries with resource limited setting.

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