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A Study of Effect of Organism Specific Sepsis on Platelet count and Platelet indices in Neonates

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Abstract

Background: Changes in platelet parameters induced by culture proven and probable neonatal sepsis have been used for an early diagnosis to prevent complications and to administer timely treatment. The role of platelet indices in sepsis has been documented in literature in adult studies however in neonates it has not been extensively studied in culture proven sepsis. We conducted this study to find out the prevalence of thrombocytopenia, MPV, PDW in culture proven neonatal sepsis.

Material and Methods: A total of 25 newborns (sepsis group) and 25 healthy newborns (control group) were evaluated in this study. The groups were analysed with regards to significant differences in the values of mean platelet volume (MPV). A p value of < 0.05 was considered statistically significant for all results.

Results: The study revealed statistically significant MPV in neonates with sepsis as compared to healthy neonates.

Conclusion: Neonatal sepsis often leads to thrombocytopenia and changes in platelet indices. It acts as one of the earliest non- specific indicator of neonatal sepsis. High MPV and PDW have a high specificity in identification of sepsis. Due to scarcity of literature with reference to organism specific response in neonatal sepsis we conducted this study to find out the prevalence of thrombocytopenia, MPV and PDW in culture proven sepsis in neonates.

Keywords: MPV, PDW,PCT

Introduction

Sepsis in newborns is one of the pre eminent causes of morbidity and mortality.[1] In developing countries neonatal mortality from sepsis is as high as 60%.[2] Changes in platelet parameters induced by culture proven and probable neonatal sepsis have been used for an early diagnosis to prevent complications and to administer timely treatment.

Neonatal sepsis is mostly associated with thrombocytopenia and late onset sepsis is one of the important cause of thrombocytopenia in neonates.[3,4,5,6,7]

It can be caused by bacterial, viral, fungal and parasitic infections and other non- infectious causes.

Platelet count less than $150x10^3/mm^3$ in any neonate is defined as thrombocytopenia despite the gestational age.[8,9] Thrombocytopenia in neonates varies from 1-5% and is much higher (22-35%) in newborns requiring intensive care. A major complication of thrombocytopenia is bleeding but it is confined to infants with platelet count less than $30,000/mm^3$.[3,10,11,12,13]

As per the studies almost 50% of culture proven sepsis cases have thrombocytopenia.[4,14] It presents as either early onset thrombocytopenia (less than 72 hours) or late onset (more than 72 hours). Early onset thrombocytopenia is mild and self limiting, it most commonly occurs due to platelet insufficiency whereas late onset thrombocytopenia which is often severe and prolonged usually is a result of bacterial sepsis and necrotizing enterocolitis.

The role of platelet indices in sepsis has been documented in literature in adult studies however in neonates it has not been extensively studied[15,16] in culture proven sepsis. Amongst the platelet indices, those related to morphology and platelet kinetics such as mean platelet volume (MPV), platelet distribution width (PDW) and plateletcrit (PCT) are studied in sepsis. MPV is a measurement of the average size of platelets found in the blood. MPV is raised in destructive thrombocytopenia and low levels are found in hypoproliferative thrombocytopenia.[17,18] Platelet distribution width is an indicator of degree of heterogeneity of platelets.

Inadequate production of platelets along with increased destruction of platelets during sepsis induced thrombocytopenia in neonates may lead to release of young platelets into the circulation. An increased proportion of young platelets may result in an increased MPV.

Until the period diagnosis is made, twenty five percent neonates have thrombocytopenia and by 36- 48 hours later, majority of them tend to have a lower platelet count. Neonates with a fungal culture positive sepsis have a greater degree of thrombocytopenia as compared to those with gram positive or gram negative bacterial sepsis.[19]

Considering the lack of literature with reference to organism specific response in neonatal sepsis, we conducted this study to find out the prevalence of thrombocytopenia, MDV, PDW in culture proven neonatal sepsis.

Materials and methods

It was an analytical cross sectional study conducted in the department of Pathology in association with Paediatrics department, Hindurao hospital from April 2016 to September 2017 after approval of institutional ethical committee.

A total of 25 patients with sepsis and 25 patients as a control group (healthy newborns) were included in the study.

Neonates greater than 37 weeks with clinical signs and symptoms of sepsis and who were blood cultures positive were included in the study. Those who received antibiotics before collection of sample, those with major congenital malformations and chromosomal anomalies were excluded from this study. Neonates who had received blood transfusion before collection of samples and those with thrombocytopenia due to congenital and acquired causes other than sepsis were also excluded from this study.

Detailed history and clinical findings were recorded. All neonates were subjected to a septic screen at the time of admission. Blood samples were collected under all septic precautions in the NICU. 2ml of blood sample was taken in EDTA vacutainer and then was processed for TLC, DLC, platelet count, MPV and PDW. Another 2ml was

taken for conventional blood culture. Automated haematology analyzer sysmex Kx-21 was used to analyze the sample and was counter checked. Thrombocytopenia was defined as platelet count less than 150,000/mm^3. Haematological parameters of all the cases were reviewed. Relevant clinical features were noted, neonates with two or more of the following clinical features were selected for sepsis evaluation-

1.) Respiratory system – tachypnea, increased apnea, severe apnea, increase ventilator support, oxygen desaturation.
2.) Cardiovascular system –bradycardia, pallor, decreased perfusion, hypotension.
3.) Metabolic changes- hypothermia, hyperthermia, feeding- intolerance, glucose intolerance, metabolic acidosis.
4.) Neurological changes – lethargy, hypotonia, decreased activity.

Statistical analysis of measurements was done using SPSS 16 software. Appropriate tests such as't' test were applied. Continuous variables were expressed as mean ± S.D. The p- value < 0.05 was considered significant.

Results

Twenty five patients with sepsis and twenty five normal newborns were included in the study. All culture positive cases were included, amongst these, fungal infection was found in nine cases (36%), Gram positive pathogens in nine cases (36%) of which four cases (16%) were coagulase negative staphylococcus aureus, one case (4%) was of methicillin resistant – staphylococcus aureus (MRSA). Seven cases (28%) were of gram negative bacterial sepsis of which five were infected with e.coli, one (4%) with klebshiella and one (4%) with pseudomonas.

Table 1- Distribution of organisms causing neonatal sepsis

	Organism	No. of cases	Percentage (%)
Gram positive	Coagulase- staph Staph MRSA	4 4 1	16% 16% 4%
Gram negative	Klebshiella E. coli Pseudomonas	1 5 1	4% 20% 4%
Fungal	Candida	9	36%
Total no. of cases		25	

Thrombocytopenia was present in 18 cases (72%) with sepsis and in only 2 (8%) cases in the control group. Minimum platelet count was 10,000/mm^3 and maximum was 190,000/mm^3 in patients with sepsis. Median value for MPV of all the cases included in this study was 12 fl. Minimum MPV was 9.1fl and maximum was 18.2fl. Median PDW value was 12.8fl, minimum value was 10.2 fl and highest value was 20.7 fl.

Table 2 – Degree of the thrombocytopenia in different organism groups-

Thrombocytopenia	Gram + ve	Gram- ve	Fungus
Severe [<50,000/mm3]		1	4
Moderate [<1,00,000/mm3-50,000/mm3]	1	1	1
Mild [<1,50,000-1,00,000/mm3]	5	3	2

>1,50,000/mm3	3	2	2
Total no. of cases	9	7	9

Table 3- Mean ± S.D of haematological parameters between control and case (with sepsis) groups-

S.No	Parameter	Control group(n=25)	Case group (with sepsis) (n=25)	P value
1.	Haemoglobin	14.852±3.14	13.068±3.94	0.083
2.	Total leucocyte count	11336.00±3124.484	11632.00±4875.51	0.799
3.	Neutrophil	49.52±14.31	55.20±20.29	0.258
4.	Absolute neutrophil count	5669.84±2541.434	6932.16±3734.72	0.428
5.	Lymphocyte	42.32±14.81	38.00±19.62	0.384
6.	Absolute lymphocyte count	4786.36±1935.43	4458.64±2958.60	0.645
7.	Eosinophil	3.80±3.32	2.60±2.12	0.135
8.	Monocyte	4.44±3.20	4.20±2.78	0.779
9.	Mean corpuscular volume	95.76±14.66	101.79±8.81	0.084
10.	Mean corpuscular haemoglobin	34.07±2.32	35.17±2.08	0.083
11.	Mean corpuscular haemoglobin concentration	34.35±1.41	34.23±1.73	0.783
12.	Platelet count	233.04±121.62	2024.88±9578.26	0.354
13.	Mean platelet volume	9.89±1.50	12.07±2.53	0.001
14.	Platelet distribution width	15.46±20.15	13.82±2.94	0.689

Discussion

Thrombocytopenia is a well known complication in critically ill patients and is associated with a higher mortality rate.[20,21] It is a common adverse effect in neonatal sepsis. Mannan et al concluded that 50% of cases of neonatal sepsis had thrombocytopenia.[14] In our study we observed lower platelet counts in 72% of cases of culture proven neonatal sepsis.

In a study done by Guida et al, thrombocytopenia was noted in 54% of culture proven neonatal sepsis cases. They also concluded that as compared to gram positive sepsis those with fungal sepsis had a significantly lower initial platelet count and increase incidence of thrombocytopenia[4] as was seen in our study. Many other studies have also shown an organism specific response of the platelets in which fungal sepsis was associated with a more prolonged thrombocytopenia[6] in contrast to a study done by Manzoni et al[22] that showed there was no difference in the incidence of thrombocytopenia amongst cases of fungal, gram negative and gram positive sepsis.[22]

Thrombocytopenia can be due to increased peripheral destruction, inadequate production or abnormal pooling.

Thrombopoeitin (TPO) is the prime regulator of megakaryocytopenia and platelet production. In neonatal sepsis, circulating TPO levels were found to be high.[23] Immune cells recognize the pathogens through toll- like receptors (TLRS). The TLRS mainly TLR-2 and TLR-4, allow the platelets to recognize the bacterial proteins during sepsis and help in regulating platelet immunity and function.[24] They are responsible in platelet activation and alter its function from hemostatic regulator to immune sentinel. Neonates with sepsis upregulate TPO production leading to increased megakaryocytopoeisis and platelet release.[25]

Platelet indices are bio markers of platelet activation. They are of diagnostic and prognostic importance in sepsis. These indices are associated with the morphology and proliferation kinetics of platelets and thus have a precise clinical usefulness in patients with sepsis. The other platelet indices include mean platelet component mean platelet mass (MPM), platelet component distribution width (PCDW), platelet large cell ratio (P-LCR) and immature platelet fraction (IPF). These indices are studied very rarely. P-LCR usually correlates with MPV but is more sensitive to changes in the platelet size.[16] IPF is increased in patients with peripheral utilisation or destruction of platelets.

Mean platelet volume (MPV) and platelet distribution width (PDW) can help in differentiating hypoplastic thrombocytopenia from consumption thrombocytopenia. Destructive thrombocytopenia is mostly associated with high MPV levels while low levels are reported in hypo-proliferative thrombocytopenia.[16] Therefore it is considered that in mild inflammation, due to rise of large platelets in the circulation, MPV levels may increase and on the other hand, levels may decrease in severe inflammation due to depletion of large platelets in inflammations area.[26] Based on these observations it was concluded that MPV may be a negative acute –phase reactant as well as a positive acute phase reactant and may show fluctuation in different phases of sepsis.

MPV is a measurement of average size of platelets and its value normally is in inverse relationship with the platelet count. It increases where there are more young platelets as a result of increased destruction. PDW is an indicator of variation in platelet size.

In this study, we noted a significant increase in MPV levels above base line values in neonatal sepsis patients. We studied the changes of platelet indices during neonatal sepsis.

In newborns mean value of MPV is 8.21+/- 0.65 and mean PDW is 17.03+/- 0.07[23-3]. In this study mean value of MPV was 12 and the mean value of PDW was 13.8.

Among all the haematological parameters studied, MPV was found to be statistically significant between sepsis patients and control group. In a study done by Guclu et al[15] MPV and PDW were the significant parameters between sepsis group and healthy newborns. Utility of MPV in predicting adverse consequences in septic shock patients had been studied by Gao et al.[16] Also the importance of MPV along with platelet count was reported by Becchi et al in sepsis patients.[27]

Our findings revealed that MPV was the significant parameter in septic patients. It was higher in septic patients than in controls. In addition to this, a lower platelet count was observed in septic patients. It occurs due to release of many cytokines, endothelial damage and bone marrow suppression in septic patients.

It has been demonstrated that in early phases of sepsis coagulation and platelet activation hyper- aggregation can occur.[27] Platelets transform into a spherical shape from

their normal discoid shape in order to occupy a large surface. Following this, pseudopodia formation occurs. Platelets with increase number and size of pseudopodia my effect PDW.[28]

In this study 36% of cases of neonatal sepsis were positive for gram positive bacterial infection of which coagulase negative staphylococcus aureus (CONS) was seen in 16% cases. Venkateshan[29] had reported 5-6% incidence of CONS in late onset sepsis where as Sanghai[30] had reported 61% of CONS cases associated with late onset sepsis

In our study, methicillin resistant staphylococcus aureus was seen in only one case (4%) and staphylococcus (SA) aureus in 16% of cases which was similar to findings of kurien et al[31] who reported SA in 13% of cases with late onset sepsis. Fungus was grown in 9 cases (36%) of sepsis in this study. Venkateshan[29] reported 11% of septic neonates with fungal sepsis and in a study by Guida et al[4] 8% of cases had fungal sepsis.

In our study, mean platelet count at the time of onset of sepsis was more in gram positive sepsis ($130x10^3/mm^3$) as compared to gram negative sepsis patients ($130x10^3/mm^3$) and in fungal sepsis patients ($86x10^3/mm^3$). Guida et al in their study found lower platelet counts in gram negative and fungal sepsis[4] and in a study done by Akarsu et al platelet counts were lower in gram negative than in gram positive sepsis.[32] Although we found higher levels of MPV and PDW in gram positive sepsis.

Also we noted absolute lymphocyte count to be statistically significant amongst gram positive and gram negative sepsis and amongst gram negative and fungal sepsis.

Conclusion

Neonatal sepsis often leads to thrombocytopenia and changes in platelet indices. It is a well known complication in culture proven neonatal sepsis. In this study 68% of the cases had lower platelet counts. Severe thrombocytopenia was more prevalent in fungal sepsis than in patients affected by gram negative and gram positive organisms. It acts as one of the earliest non-specific indicator of neonatal sepsis.

(MPV) mean platelet volume and (PDW) platelet distribution width are important parameters in assessing the mechanism of platelet destruction. High MPV and PDW have a high specificity in identification of sepsis.

Platelet indices are of diagnostic and prognostic significance in sepsis therefore it should be carefully monitored in these patients.

Due to scarcity of literature with reference to organism specific response in neonatal sepsis we conducted this study to find out the prevalence of thrombocytopenia, MPV and PDW in culture proven sepsis in neonates.

Declarations

Consent for publication- Written informed consent was obtained from the guardians for publication of this research study. Ethical and research committee of Hindurao Hospital approved the study and clearance was given.

Competing interests- None.

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