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A study on platelet count and their indices as a marker of neonatal sepsis

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Abstract
Objectives

- Effect of sepsis on platelet counts and their indices.
- Monitoring of platelet count and their indices in neonatal sepsis in relation to specific organisms.
- To identify organism involved in proven neonatal sepsis affecting platelet indices.

Design: Prospective hospital based study.
Setting: The study subjects are all neonates admitted in Shadan Institute of Medical Sciences and has proven sepsis.
Method: The study was carried out over a period of one and half year from December 2019 to July 2020 at Shadan Institute of Medical Sciences. 100 cases were considered for this study after proper screening for CBC, platelet count and their indices like mean platelet volume, platelet distribution width and CRP and blood culture in neonates admitted in our NICU with proven sepsis.
Results: A total of 100 neonates with blood culture positive for bacterial cases were considered for the study. Early onset septicaemia (59%) was more common than late onset septicaemia (41%). Out of 100 cases 57% cases had growth of gram negative organisms, 40% had growth of gram positive organisms and 3% had growth of fungal. Tachypnea (27%), Lethargy (20%) and refusal of feeds (8%) were the commonest clinical presentation followed by, Fever (6%), convulsions (5%) and jaundice (5%). 60% neonates has thrombocytopenia of varying severity. *Staphylococcus aureus* was the most common organism associated with thrombocytopenia (43.3%%). MPV was high in 85% of cases and PDW was high in 96% of cases.
Conclusion: The present study highlights the association of thrombocytopenia, mean platelet volume and platelet distribution width with causative organism in proven neonatal sepsis. *Staphylococcus aureus* was the most common organism causing thrombocytopenia in our NICU.

Keywords: neonatal sepsis; thrombocytopenia, *Staphylococcus aureus*, MPV, PDW.

Introduction

Neonatal septicemia is a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteremia in the first month of life [1].
Sepsis is a common complication in the neonatal intensive care unit and is a major cause of neonatal mortality. It is caused by various organisms invading the blood stream, which may be by bacterial, viral, fungal and protozoal infections.
It is characterized by positive blood culture, thrombocytopenia and elevated C-reactive protein. Septic shock is the most dangerous complication of septicaemia [1].
Thrombocytopenia (platelet count < 150,000/μL) is one of the most common haematological problems in Neonatal Intensive Care Units (NICUs), with 18- 35% of the NICU patients developing this problem before hospital discharge.
In contrast, only 2% of the neonates are thrombocytopenic at birth with Severe Thrombocytopenia (platelet count < 50,000/μL) occurring in less than 3/1000 term infants.[2]

Megakaryopoiesis and thrombopoiesis and platelet physiology in the fetus and neonate:
Platelets are small anucleate fragments that are formed from the cytoplasm of megakaryocytes and have a characteristic discoid shape [3]. Megakaryopoesis include the production of megakaryocytes from stem cells, while thrombopoiesis is the production of platelets from megakaryocytes.
Platelet production begins in the yolk sac and, like the remainder of hematopoiesis shifts to the fetal liver and then to the marrow at the time of gestation [4].

The most primitive progenitor cell that gives rise to megakaryocytic lineage cells is the multipotent progenitor, CFU-GEMM (Colony forming unit-granulocyte I erythrocyte / monocyte / megakaryocyte) [5]. The most primitive progenitor cell committed exclusively to the megakaryocytic lineage is BFU-MK (Burst forming unit megakaryocyte) [5].

Platelet counts, size and survival

Platelet counts in newborns are similar to those in adults with values of 150000- 450,O0O/μL.

Platelet counts of the adult range are already encountered in the fetus by the IInd trimester.

So by implication, however premature a neonate may be a platelet count below 150,00O/μL cannot be considered to be normal. The size of the platelet in the term and premature infant averages 7-9 fl similar to the adult normal range.[3]But one study has reported a greater MPV in term than preterm infants [3]. Castle *et al* measured 1n-oxine labeled platelet survival and observed that thrombocytopenic babies had decreased platelet survival time compared to that of normal adults**.**

Classification

- Some authors classify Neonatal Thrombocytopenia into
- Mild (<150,000/μL and ≥ 100, 000/μL),
- Moderate(<100,000/μL and ≥ 50,000/μL),

Severe (<50,000/μL). Based on the underlying mechanism of neonatal thrombocytopenia can be classified as [4]

- Impaired platelet production
- Increased consumption
- Combined mechanism

Classification of neonatal thrombocytopenia based on time of onset

- Early onset thrombocytopenia.
- Late onset thrombocytopenia.

Objectives

- Effect of sepsis on platelet counts and their indices.
- Monitoring of platelet count and their indices in neonatal sepsis in relation to specific organisms.
- To identify organism involved in proven neonatal sepsis affecting platelet indices.

Study subjects

The study subjects are all neonates admitted in Shadan Institute of Medical Sciences, Hyderabad and has proven sepsis.

Inclusion criteria

All neonates admitted in our NICU with proven sepsis.

Exclusion criteria

1. Causes of thrombocytopenia other than sepsis
2. Neonates whose parents or guardians did not agree to be a part of study.

Study Design

Prospective hospital based study.

Study Period

The study was carried out over a period of one and half year from December 2019 to July 2020 at Shadan Institute of Medical Sciences, Hyderabad.

100 cases were considered for this study after proper screening for CBC, platelet count and their indices like mean platelet volume, platelet distribution width and CRP and blood culture in neonates admitted in our NICU with proven sepsis.

Volume of blood

The chance of growing an organism effectively increases following inoculation of 0.5 ml venous blood in a pediatric blood culture bottle or 1 ml in an adult blood culture bottle (if the pediatric bottle is not available).

The anticoagulant recommended for the blood culture is sodium Polyanethol Sulfonate (SPS Liquiod) in concentration of 0.0025% to 0.003%.

Methods of collection of blood

Collecting a blood sample for culture was carried out under strict aseptic conditions to avoid contamination.

Sterile gloves were worn prior to the procedure and a patch of skin approximately 5cm in diameter over the proposed veni-puncture site was prepared. This area was cleaned thoroughly with alcohol followed by povidine-iodine followed again by alcohol. Application of povidine-iodine was done in concentric circles moving outwards from the centre to avoid contamination.

The skin was allowed to dry for at least minute before sample is collected.

Once blood was drawn and inoculated in to the appropriate media, it was immediately sent to the microbiology laboratory for incubation. Blood culture bottles or tubes were never inoculated when the medium was cold nor were they refrigerated after inoculation.

This technique measures the CO2 derived pH changes by a colometric sensor in the bottom of each bottle.

The sensor is separated from the broth medium by a membrane that is only permeable to CO2.

As organisms grow they release CO2 which diffuses across the membrane and is dissolved in water present in the matrix of the sensor. As CO2 is dissolved, free hydrogen ions are generated. These freely generated hydrogen ions cause a colour change in the sensor which is read by the instrument.

Culture techniques

BacT/ALERT automated blood culture system is used to determine the growth of the organism.This technique measures the CO2 derived pH changes by a colometric sensor in the bottom of each bottle.

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These freely generated hydrogen ions cause a colour change in the sensor which is read by the instrument.

Within 6-18 hours of incubation most bacteria responsible for a clinically significant disease are present in numbers large enough to give a positive signal.66 Quick screening methods like quantitative direct plating (QDP) by placing

few drops of blood may be useful where bacteraemia is of high degree or in neonates. Other sophisticated techniques in rapid isolation of organisms are by the use of radio-labelled carbon (14C) and automated techniques are recommended by some. Blood culture reports were declared at 3-5 days of incubation period. Those babies with proven bacterial sepsis were included in the study and platelet counts, bleeding manifestations and causative organisms were noted. 2ml venous blood samples were taken in EDTA bulbs for platelet count analysis using automated analyser.

Table 4: Distribution of Patients according to age and sex

Age in hours	Males		Females		Total	
	No.	%	No.	%	No.	%
24 hours	33	50.7	20	57.1	53	53.0
48 hours	6	9.2	3	8.6	9	9.0
72 hours	7	10.8	4	11.4	11	11.0
96 hours	6	9.2	3	8.6	9	9.0
120 hours	5	7.7	2	5.7	7	7.0
>120 hours	8	12.4	3	8.6	11	11.0
Total	65	100.0	35	100.0	100	100.0
Mean ± SD	74.51 ± 64.52		71.03 ± 53.49		72.46 ± 57.23	
t-test value	t = 0.78				---	
P-value & Significance	P = 0.34 NS				---	

The study reveals that, most patients 53 (53.0%) presented within 24 hours of age, followed by 11 (11.0%) patients who presented after 48 hours of age.

The minimum age of a patient was 1 day (24 hours) and maximum age of a patient was 9 days.

The Mean and SD of age of males was 74.51 ± 64.52 hours and females was 71.03 ± 53.49 hours. Overall Mean age of all patients was 72.46 ± 57.23.

There was no statistically significant difference of age of patients among males and females (P>0.05). The sex ratio of male to female in the study was observed to be 1.85:1

Table 5: Organism Causing Neonatal Sepsis

Variable	Organisms	No. of patients	%
Gram-Positive 40 (40.0%)	Staph aureus	37	37.0
	CoNS	2	2.0
	Enterococcus	1	1.0
Gram-Negative 57 (57.0%)	*E coli*	24	24.0
	Klebsiella	24	24.0
	Pseudomonas	9	11.6
Fungal 3 (3.0%)	Candida	3	3.0
Total	--	100	100.0

The study reveals that, most of the organisms isolated were Gram-negative (57%), followed by gram positive(40%) and fungal (3%).

Table 6: Distribution of Neonatal sepsis based on place of delivery

Sepsis		No. of patients	%
Intramural	BTGH	34	34.0
	STGH	11	11.0
	Sub Total	45	45.0
Extramural	Private hosp.	29	29.0
	Primary Health centre	16	16.0
	Govt. General Hosp	9	9.0
	Home Delivery	1	1.0
	Sub Total	55	55.0
Grand Total		100	100.0

It was observed that, Intramural patients were 45 (45.0%) and Extramural patients were 55(55.0%). In our study sepsis due to patients born outside hospital were more than those inside the hospital. Of the extramural, patients born in private hospital were 29% followed by primary health centre(16%),govt general hospital(9%) and home delivery(1%).

Table 7: Distribution of Neonatal Sepsis based on age of onset

Sepsis	No. of patients	%
EOS	59	59.0
LOS	41	41.0
Total	100	100.0

In the study EOS were 59 (59.0%) and LOS been 41 (41.0%) patients. EOS more common than LOS.

Table 8: Distribution of patients according to clinical presentation

Sepsis		No. of patients	%
RDS		27	27.0
Lethargy		20	20.0
Preterm	LGA	6	6.0
	AGA	21	21.0
	SGA	3	3.0
	Total	30	30.0
Poor feeding		7	8.0
Fever		6	6.0
Convulsions		5	5.0
Icterus		5	5.0
Abdominal Distension		3	3.0
Birth asphyxia		3	3.0
MAS		2	2.0
Excessive crying		2	2.0
Vomiting		2	2.0
Decreased activity		1	1.0
Excessive Frothing		1	1.0
H/0 Aspiration		1	1.0
Ruptured meningocele		1	1.0
Shallow Respiration		1	1.0

In our study most common presentation is tachypnea, followed by lethargy,

Table 9: Demographic data of neonatal sepsis

Variables	All Patients N=100	Gram- Positive (N=40)	Gram- Negative (N=57)	Fungal (N=3)	ANOVA Test Value	P-Value & Sig.
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD		
Gestation age in wks	36.56 ± 2.37	36.63 ± 2.39	36.30 ± 2.36	34.61 ± 1.88	F = 0.58	P=0.561 NS
Birth weight in kgs	2.27 ± 0.60	2.26 ± 0.58	2.29 ± 0.62	1.30 ± 0.0	F = 0.33	P=0.764 NS
Neonatal age in hours	72.46 ± 57.23	81.47 ± 62.12	59.74 ± 39.81	56.10 ± 45.23	F = 2.39	P=0.019 S
Hospital stay in days	16.34 ± 5.78	16.88 ± 5.32	15.79 ± 6.12	12.12 ± 7.03	F = 0.89	P=0.382 NS
Hb% level	14.86 ± 2.64	14.6 ± 2.55	15.17 ± 2.79	13.82 ± 3.19	F = 1.73	P=0.353 NS
Total count	23643 ± 38657	23824 ± 40472	23029 ± 34031	16065 ± 44031	F = 0.38	P=0.731 NS
Caesarean section	39 (39.0%)	14 (35.0%)	24 (42.7%)	2 (33.3%)	X^2=1.34	P=0.743 NS

There was no statistically significant difference of mean Gestation age, Birth weight, Hospital stay, Hb% level and Total count among Gram-positive, gram- negative and fungi. There was statistically significant difference of neonatal age of patients among gram-positive, gram-negative and fungal (P<0.05).

Table 10: Distribution of Neonatal Thrombocytopenia according to causative organisms

Variable	Organism	No.	%
Gram-Positive 27/60 (45%)	Staph aureus	26	43.3
	CoNS	1	1.7
Gram-Negative 30/60 (50%)	*E coli*	13	21.7
	Klebsiella	12	20.0
	Pseudomonas	5	8.3
Fungal 3/60 (5%)	Candida	3	5.0
Total	---	60	100.0

The study reveals that, 60 (60.0%) patients had neonatal Thrombocytopenia. Out of 60 cases of Neonatal Thrombocytopenia, most common causative organism was *Staphylococcus aureus* (43.3%) followed by *E coli* (21.7%), Klebsiella (20.0%) Pseudomonas (8.3%) and candida (5%).

Table 11: Platelet count (per µl) at onset of sepsis in the groups

Variables	Platelet count (per µl) Mean ± SD	Test Values	P-Value & Significance
Gram-Positive	164960 ± 68083	F = 3.12	P=0.043 S
Gram-Negative	212870 ± 103540		
Fungal	143667 ± 18625		
Total	180479 ± 93754	---	---

The Mean and SD of Platelet count (per µl) of patients with gram positive septicaemia was164960 ± 68083, gram-negative septicaemia was 212870 ± 103540 and fungal septicaemia was 143667 ± 18625. Overall Mean and SD of Platelet count (per µl) was 180479 ± 93754.

There was statistically significant difference of Platelet count (per µl) among gram-positive and negative and Fungi patients (P<0.01).

Table 12: Drugs Sensitivity in Neonatal Sepsis

Drugs	Gram- Positive		Gram- Negative		Fungi		Total	
	No.	%	No.	%	No.	%	No.	%
Ampicillin	2	2.0	3	3.0	0	0	5	5.0
Amikacin	5	8.0	7	4.0	0	0	12	12.0
Cefoperazone	2	2.0	3	3.0	0	0	5	5.0
Cefotaxime	5	6.0	6	2.0	0	0	11	11.0
Chloramphenicol	0	1.0	3	2.0	0	0	3	3.0
Colistin	0	2.0	2	0.0	0	0	2	2.0
Gentamycin	0	1.0	2	1.0	0	0	2	2.0
Imipenem	10	10.0	1	1.0	0	0	11	11.0
Levofloxacin	0	1.0	1	0.0	0	0	1	1.0
Linezolid	6	6.0	1	1.0	0	0	7	7.0
Meropenem	4	21.0	21	21.0	0	0	25	25.0
Piperacillin+tazobactam	2	3.0	2	1.0	0	0	4	4.0
Vancomycin	7	17.0	2	4.0	0	0	9	9.0
Vancomycin, linezolid	14	13.0	0	4.0	0	0	14	14.0
All resistant	0	0.0	1	1.0	0	0.0	1	1.0

The study reveals that, most organisms were sensitive to Meropenem (25%) followed by vancomycin (21.0%) and linezolid (12.0%).

In the study 21% of gram negative organisms, 4% of gram positive organisms are sensitive to meropenem, 17% of gram positive organisms, 4% of gram negative are sensitive to vancomycin and 6% of gram positive organisms, 1% of gram negative organisms are sensitive to linezolid.

Table 13: Effect of Different Organisms on Platelet Indices in Neonatal Sepsis.

	Organism	No. of patients	Platelet count at onset of sepsis (per µl)	Lowest platelet count (per µl)	Average MPV (Fl)	MPV Range	PDW	PDW Range
Gram- Positive 27/60 (46.5%)	Staph aureus	26	97300	15000	10.38	9.6-13.3	15.82	14.2- 17.4
	CoNS	1	148000	60000	13.3	13.3	16.4	16.4
Gram- Negative 30/60 (48.8%)	*E coli*	13	112400	11000	9.82	8.6-12.5	14.73	14.1- 16.3
	Klebsiella	12	98250	28000	10.56	8.9-13.7	15.46	14.9- 16.8
	Pseudomonas	5	138000	104000	9.65	9.9-11.2	14.3	14.0- 15.5
Fungi 3/60 (4.7%)	Candida	3	131000	60000	10.1	9.2-13.3	14.51	15.3- 16.5
Total	--	60	-	-	-		-	

The study reveals that lowest platelet count is found in patient in whom E-coli isolated was 11000 followed by *Staphylococcus aureus* (15000), klebsiella (28000), candida (60000) and pseudomonas (104000). Organism causing severe thrombocytopenia was E-coli followed by *Staphylococcus aureus* and klebsiella.

In our study mean platelet volume was 13.3 in CoNS, 10.56 in klebsiella, 10.38 in *Staphylococcus aureus*, 10.1 in candida, 9.82 *E coli* and 9.65 in pseudomonas.

Our study also reveals, platelet distribution width was 16.4 in CoNS, 15.82 in *Staphylococcus aureus*, 15.46 in klebsiella, 14.73 in E coli, 14.51 in candida and in pseudomonas.

Table 14: Degree of Neonatal Thrombocytopenia

Sepsis	Thrombocytopenia			Total
	Mild (1,00,000-1.5L)	Moderate (50,000-1,00,000)	Severe (< 50,000)	
Present	43 (71.7%)	13 (21.6%)	4 (6.7%)	60 100.0%)

The study reveals that, Maximum number of patients 43 (71.7%) had mild Thrombocytopenia, followed by 13 (21.6%) patients had moderate Thrombocytopenia and 4 (6.7%) patients had severe Thrombocytopenia.

Table 15: Comparison of sepsis and Platelet Distribution width (PDW)

Sepsis	Platelet Distribution width (PDW)			Total
	Decreased ≤ 7.5	Normal 7.5-11.5	Increased > 11.5	
Present	0 (0.0%)	4 (4.0%)	96 (96.0%)	100 (100.0%)

The study reveals that, Maximum number of patients - 96 (96.0%) patients had increased Platelet Distribution width (PDW).

Table 16: Comparison of sepsis and Mean Platelet volume (MPV)

Sepsis	Mean Platelet volume (MPV)		Total
	Increased	Decreased/Normal	
Present	85 (85.5%)	15 (15.0%)	100 (100.0%)

The study reveals that, Maximum numbers of patients 85 (85.0%) patients had increased MPV.

Discussion

More than 30-80%of neonates with proven infection become thrombocytopenic. Bacterial, fungal and viral infections all have been associated with neonatal thrombocytopenia. Thrombocytopenia occurs in one-third of infants admitted in neonatal intensive care unit. Thrombocytopenia is frequently associated with mucosal bleeds and purpura.

Fungal sepsis is associated with greater degree of thrombocytopenia than is seen with gram positive or gram negative organisms and outcome in these neonates is poor[6]. MPV levels may increase in mild inflammation because of the raise of large platelets, or on the contrary, MPV levels may decrease in severe inflammation owing to the depletion of large platelets in inflammatory area [7]. Destructive thrombocytopenia known to be associated with high MPV levels while low level of MPV is reported in hypo-proliferative thrombocytopenia [8]. These observations indicate 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.

In our study we made an attempt to see association of platelet count and their indices in neonatal sepsis.

Comparison of Cases according to sex

Sex Incidence in our study was of male predominance.

In our study Male/Female ratio is 1.8:1.

Our study result is consistent with Woranart *et al* study which showed that males had higher incidence than female neonates [9].

According to onset of sepsis

In our study EOS (59%) is more common than LOS (41%). Antoniette B *et al* reported early onset of sepsis within 24 hours in 85% cases [10].

Clinical Presentation

In the present study Respiratory distress (27%) and lethargy (20%) were the commonest clinical presentation followed by Refusal of feeds (8%), Fever (6%), convulsions (5%) and Icterus (5%).

Lethargy, refusal of feeds and respiratory difficulties were the commonest presenting combination of complaints [11].

Ahsan Ahmad *et al*, reported that fever (46%) was the most frequent symptoms, followed by respiratory difficulties (39%), lethargy (37%), refusal of feeds (33%), jaundice (21%) and convulsions (18%) [12].

Comparison of organism in different studies

In our study 6 organisms was isolated and all these organisms were associated with some form of thrombocytopenia. Among them gram negative sepsis (57%) is more common than gram positive sepsis. In gram negative sepsis (57%) most common organism is klebsiella pneumonia (24%), *E coli* (24%) followed by pseudomonas (9%). In gram positive organism (40%) *Staphylococcus aureus* (37%) was the most common organism causing sepsis.

Parvez Rajnesh13 proved in their study that gram negative organisms causing sepsis were 54%. In that most common were Klebsiella, followed by pseudomonas then acinetobacter and gram positive were 40%, of which staphylococcus was most common followed by Enterococcus.

Platelet Count Comparision

In our study most common organism causing thrombocytopenia is staphylococcus (43.3%) next in the line here *E. coli* (21.7%), Klebsiella (21%), pseudomonas(8.3%) candida (5%) and CONS(1.7%). Gram negative organisms are the most common organisms causing thrombocytopenia (50%) than gram positive organisms (45%) and fungal organisms (5%)

Jack D Guida's study, [14] Gram negative were 16% whereas grams positive and fungal were 7.6% and 8%, respectively.

Mean Platelet Volume

In our study Decreased platelet count associated with increase in MPV (85%).

Nelson and Kehl *et al* observed platelet consumption associated with increase in MPV in human subjects having acute infection [15].

Becchi *et al* suggested that MPV has an important prognostic value of early stage of sepsis [16].

Platelet Distribution Width

In our study there is a increase in PDW in 96% of cases. Patrick CH *et al*., reported that there is significantly increased presence of bacteremia in those neonates with MPV greater than 10.8fl and/or PDW greater than 19.1%. [17]

Conclusion

Neonatal sepsis has vague signs and symptoms, so high index of suspicion helps in arriving at early diagnosis and management of sepsis. Neonatal sepsis was common in males. Gram positive organisms were the predominant causative agents of septicaemia 40% as compared to gram negative organisms 57% and fungal sepsis 3%. *Staphylococcus aureus* was the commonest organism responsible for thrombocytopenia. Among thrombocytopenic neonates 43% had mild thrombocytopenia, 13% had moderate thrombocytopenia and 4% had mild thrombocytopenia.

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Conflict of Interest

None

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