Original Research Paper

Volume - 10 | Issue - 10 | October - 2020 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Neonatology

PLATELET COUNT IN CULTURE POSITIVE NEONATAL SEPSIS AND ITS CORRELATION WITH SPECIFIC CAUSATIVE ORGANISM- A PROSPECTIVE COHORT STUDY.

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ABSTRACT

Introduction: In neonates admitted with sepsis, thrombocytopenia is one of the common hematological problems encountered. It is commonly seen in both gram negative and gram positive septicemia. Thrombocytopenia may be considered as an important early indicator in prediction of septicemia in neonates admitted in NICU.

Methods: This study was conducted in Level IIB NICU of Shri B M Patil Medical College Hospital Vijayapur, Karnataka. Study Design: Prospective Observational study was conducted. Study Duration: 1 year (Jan 2019 – Jan 2020). Inclusion Criteria: Neonates admitted in NICU with Culture Positive Sepsis were included in the study. Exclusion Criteria: Neonates with maternal history suggestive of placental insufficiency and low platelet counts and family history of bleeding disorders.

Results: Out of 1250 admissions in NICU, 180 neonates had culture positive sepsis. Among 54% gram negative organisms, Klebsiella pneumonia was the commonest seen in 56% neonates. Among 40% gram positive organism MRSA was the commonest 53% neonates. Among 6% Fungal Sepsis, Candida sp. (100%) isolated. Severe thrombocytopenia was seen in 16% neonates followed by moderate thrombocytopenia (37%), mild thrombocytopenia (28%) and normal platelet count (19%). The total mortality was high (22%) in neonates having sepsis. Mortality was higher in the neonates having severe thrombocytopenia (69%) compared to neonates having moderate thrombocytopenia (30%) (P value <0.001). Klebsiella pneumoniae (60%) was the leading cause of death in the neonates with sepsis.

Conclusions: Major cause of mortality in neonates with sepsis was by Gram Negative sepsis followed by Fungal and Gram Positive sepsis. Proportion of thrombocytopenia in neonates admitted with sepsis was high. Thus thrombocytopenia can be considered as one of the earliest nonspecific predictor of sepsis in neonates admitted in NICU and also it associates significantly with the outcome of the septic neonates.

KEYWORDS : Sepsis; Thrombocytopenia; Gram negative organisms; Blood Culture.

INTRODUCTION

Neonatal sepsis contributes to leading cause of mortality in developing countries (50-60%).[1] According to International Sepsis definition conference, Sepsis is defined as clinical syndrome characterized by presence of both infection and systemic inflammatory response syndrome (SIRS). Conventionally, neonatal sepsis has been classified as early onset sepsis (EOS) and late onset sepsis (LOS) with 72 h of life as a common demarcation.[2]

In sick neonates admitted in NICU, thrombocytopenia is one of the common hematological problems encountered and signifies an underlying disease process. Low Platelet Count is observed in most of the sick, low birth weight and premature neonates either in early or late onset sepsis. It is commonly seen in both gram negative, gram positive and fungal septicemia and low platelet is usually seen even before the pathogens are cultured from the blood. Therefore, thrombocytopenia may be considered as an important and early tool in diagnosis of septicemia in neonates admitted in NICU.[3]

In neonates, thrombocytopenia presents either as early onset (less than 72 hours) or late onset thrombocytopenia (more than 72 hours). Early onset thrombocytopenia is most commonly due to platelet insufficiency and is mild and self-limiting while late onset thrombocytopenia is commonly due to bacterial sepsis and necrotizing enterocolitis and is often severe and prolonged. Causes of thrombocytopenia in septic neonates can be broadly due to increased platelet destruction, decreased platelet production or mixed etiology.[4]

Hence, in view of the high incidence of mortality due to neonatal sepsis in relation with thrombocytopenia in neonates admitted in NICUs. This study was done to find out association between the two factors and also the effect of different organisms on various platelet parameters in neonates.

METHODS

This study was conducted in Level IIB NICU of Shri B M Patil Medical College Hospital Vijayapur, Karnataka over a period of 1 year. Informed written consent was taken from the parents/guardians of all neonates enrolled in the study. Study Design: Prospective Observational study.. Study Duration: 1 year (Jan 2019 – Jan 2020). Ethical Committee Clearance was taken before commencement of the study. Inclusion Criteria: Neonates admitted in NICU with Culture Positive Sepsis were included in the study. Exclusion Criteria: Neonates with maternal history suggestive of placental insufficiency and low platelet counts and family history of bleeding disorders were excluded from the study.

Neonates admitted to NICU during the study period with features of Sepsis underwent Complete blood count, Rapid screening tests (Absolute Neutrophil count, Immature to total neutrophil ratio, micro ESR and CRP) and Blood culture as per unit protocol. Data was collected regarding demographic profile, type of sepsis (early onset/late onset), presentation (non-specific/systemic), hematological parameters and organism isolated. All the data was documented in a pre-structured proforma and data was analyzed as per standard statistical methods. An outcome in the form of death before discharge was analyzed.

Definitions and Criteria used in this Study:

Culture positive Sepsis: Neonate with clinical features suggestive of Sepsis, Pneumonia or Meningitis with isolation of pathogen from blood.

EOS (Early Onset Sepsis):

Clinical features suggestive of Sepsis appearing within 72 h of birth, while in LOS (Late onset sepsis): Clinical features of sepsis seen after 72 hours of birth. Normal platelets count: defined as platelet count is >150,000/mm^3. Thrombocytopenia was defined as neonates having platelets counts<150,000/mm^3.

Mild, Moderate and Severe thrombocytopenia were defined as platelets counts between 100,000-150,000/mm^3, 50,000-100,000/mm^3 and <50,000/mm^3 respectively. The duration of thrombocytopenia was the number of continuous days during which the platelet count persisted<150,000/mm^3. Platelets nadir was the lowest platelet count documented of the neonate from the period, blood culture was drawn.

Blood Samples:
were collected from a peripheral vein with proper aseptic precautions before starting any antibiotic therapy. Prepared a patch of skin approx. 5-cm in diameter over the proposed venipuncture site. This area was cleansed thoroughly with 70% alcohol followed by povidone-iodine (1%), followed again by 70% alcohol. Application of povidone- iodine and alcohol was done in concentric circles moving outward from the centre. The skin was allowed to dry for at least 1 minute before the sample was collected. A 1 ml sample of blood was taken for a blood culture bottle containing 5-10 ml of culture media. Blood cultures were collected from a fresh venipuncture site. All blood cultures were incubated at 37°C and observed for 72 hours for growth of micro-organism.

Statistical Analysis
The data was analyzed by using software SPSS version 23. Association and correlation of qualitative data were tested by chi-square test and Fischer's exact test was applied in quantitative data. A P value <0.05 was considered statistically significant.

RESULTS

Out of 1250 admissions in NICU, 180 (14.4%) neonates had culture positive sepsis. Out of these 180 neonates enrolled, 77 (43%) were females and 103 (57%) were males. 73(40%) newborns were having normal birth weight, 51 (28%) were having low birth weight, 39 (22%) were having very low birth weight and 17(10%) were extremely low birth weight.54 (30%) newborns were delivered via normal vaginal delivery, 17(9%) via assisted NVD and 109(61%) via lower section caesarean section respectively. 124(69%) newborns were between 34-40 weeks gestation, 40(22%) were 28-34weeks gestation, 16(9%) were <28 weeks gestation respectively. 123(68%) newborns were Appropriate for gestational age, 45(25%) newborns were Small for gestational age, 12(7%) were large for gestational age. Baseline Characteristics of 180 neonates enrolled in the study showed no statistically significant difference among the study groups. (Table-1)

Table 1: Baseline Parameters In Neonatal Sepsis.

Baseline Paramaters		Gram negative (n=98)	Gram Positive (n=72)	Fungus (n=10)	p value
GENDER	Male	56	40	07	0.688
	Female	42	32	03	
BIRTH WEIGHT (KG)	<1	09	05	03	0.178
	1-1.5	22	14	03	
	1.5-2.5	29	20	02	
	>2.5	38	33	02	
GESTATIONAL AGE	<28wks	09	05	02	0.305
	28-34wks	22	14	04	
	34-40wks	67	53	04	
MODE OF DELIVERY	NVD	30	20	04	0.742
	Assisted	07	09	01	
	LSCS	61	43	05	
APPROPRAIATE FOR GESTATIONAL AGE	AGA	69	48	06	0.894
	SGA	22	20	03	
	LGA	07	04	01	

Among 180 newborns enrolled, 116(64%) cases had early onset sepsis, while 64 (36%) had late onset sepsis. Among 98(54%) gram negative organisms, *Klebsiella pneumonia* was seen in 55(56%), *Pseudomonas* 14(14%), E. Coli 12 (12%) and *Acinetobacter* 10(10%).Among 72 (40%) gram positive organism MRSA was the commonest 38 (53%) followed by *Enterococcus* 17 (23%) and Coagulase negative *staphylococci* 9(13%). Among 10 (6%) Fungal Sepsis, *Candida sp.*10 (100%) isolated. (Table2).

Table 2: Organisms Isolated In Neonatal Sepsis

Organisms		Frequency	Percentage %
Gram Postive Organisms(n= 72)	MRSA	38	53
	Coagulase Negative Staphylococci (CONS)	9	13
	Enterococci sp.	17	23
	Streptococcus Pneumoniae	8	11
Gram Negative Organisms (n=98)	Klebsiella	55	56%
	Acinetobacter	10	10%
	Escherichia Coli	12	12%
	Pseudomonas	14	14%
	Enterobacter	5	5%
	Proteus	2	3%
Fungus (n=10)	Candida Sep	10	100%

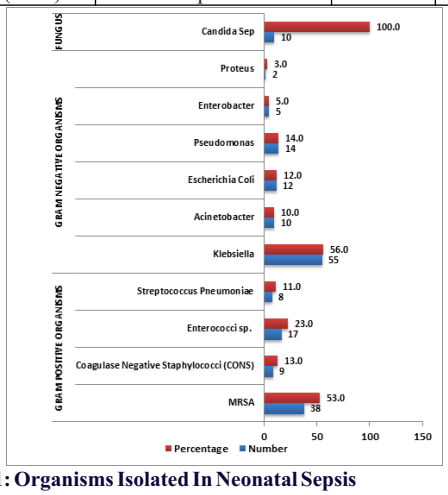

Figure 1: Organisms Isolated In Neonatal Sepsis

Mean birth weight in gram positive organism was 1.95±0.76, in gram negative organism was 2.05±0.97and in fungal sepsis it was 1.45±0.87 (p= 0.112). Average gestational age in gram positive organism 36.78±2.45, in gram negative 35.89±4.56 and in fungal sepsis 35.38±3.18 (p=0.247).

There was no statistically significant difference in terms of gestational age, premature rupture of membranes, maternal fever, meconium stain, Necrotizing enterocolitis, Gastro intestinal bleed and pulmonary hemorrhage among different groups of organisms. (Table-3)

Table 3: Various Parameters In Neonatal Sepsis

	Gram Negative (n=98)	Gram Positive (n=72)	Fungus (n=10)	P Value
Birth Weight	2.05±0.97	1.95±0.76	1.45±0.87	0.112
Gestational Age	35.89±4.56	36.78±2.45	35.38±3.18	0.247
PROM	24	16	02	0.912
Maternal Fever	15	11	00	0.842
Meconium Stained Liquor	20	19	00	0.441
Necrotizing Enterocolitis	19	14	03	0.718
Pulmonary Hemorrhage	09	07	02	0.552
G I BLEED	29	22	02	0.789

Note: * significant at 5% level of significance (p<0.05)

Mean platelet count at onset of sepsis in gram positive organism was 108000±26000 while in gram negative organism was 76000±32000 and in Fungal sepsis was 66000±28000 (P<0.001). Severe thrombocytopenia was seen in 29(16%) newborns followed by moderate thrombocytopenia in 67(37%) newborns and mild thrombocytopenia in 50(28%) newborns with normal platelet count 34(19%). Platelet nadir was 24000/µl in gram negative sepsis, 16000/µl in fungal sepsis and 28000/µl in gram positive sepsis. (p=<0.001). The mean duration of thrombocytopenia was3.7 days in gram positive sepsis, 7.8 days in gram negative sepsis and 6.5 days in fungal sepsis. (p=<0.001). (Table-4)

Table 4: Platelet Indices In Neonatal Sepsis.

Lab Parameters		Gram Negative (n=98)	Gram Positive (n=72)	Fungus (n=10)	P-Value
Platelet Count at admission		142000± 47000	157000± 37000	145000± 51000	0.085
Platelet Count at onset of Sepsis		76000± 32000	108000± 26000	66000± 28000	<0.001*
Platelet count At 72 hours of sepsis	>1,50,000	14	20	00	<0.001*
	1,00,000-1,50,000	18	30	02	

	50,000-1,00,000	42	20	05	
	<50,000	24	02	03	
Duration of Thrombocytopenia (Days)		7.8	3.7	6.5	<0.001*
Platelet Nadir		24000	28000	16000	<0.001*

Note: * significant at 5% level of significance (p<0.05)

Among 29(16%) Severe thrombocytopenic newborns, *Klebsiella pneumoniae* 48% (14) were commonest organism, followed by *Pseudomonas sp.*21% (6) and *Staph. aureus* 7% (Table-5).

Table 5: Association Of Platelets Counts With Organisms Isolated.

ORGANISM	Severe Thrombocytopenia	Moderate Thrombocytopenia	Mild Thrombocytopenia	Normal Platelet count
Gram Negative Sepsis				
Klebsiella	14	22	08	11
Pseudomonas	06	04	04	00
Acinetobacter	01	08	01	00
Escherichia Coli	02	05	03	02
Enterobacter	01	02	01	01
Proteus	00	01	01	00
Gram Positive Sepsis				
MRSA	02	12	16	08
Enterococci sp.	00	05	08	04
Coagulase Negative Staphylococci (CONS)	00	01	03	05
Streptococcus Pneumoniae	00	02	03	03
Fungal Sepsis				
Candida Sep	03	05	02	00

The total mortality was high 22% (40/180) in newborns having sepsis. Mortality was higher in the newborns having severe thrombocytopenia 69% (20/40) compared to newborns having moderate thrombocytopenia 30% (20/40) (P value <0.001) (Table-6).

Table 6: Association Of Platelets Count With Neonatal Outcomes.

Platelet Count	DISCHARGE (140)	DEATH (40)	P Value
Severe Thrombocytopenia (N=29)	09(31%)	20 (69%)	<0. 001*
Moderate Thrombocytopenia (N=67)	47(70%)	20(30%)	<0. 001*
Mild Thrombocytopenia (N=50)	50(100%)	00(00%)	<0. 001*
Normal Platelet Count (N=34)	34(100%)	00(00%)	<0. 001*

Note: * significant at 5% level of significance (p<0.05)

Klebsiella pneumoniae 24 (60%) was the leading cause of death in the newborns followed by *Pseudomonas spp*. 5 (13%), *E- coli 2* (5%), *Staph. aureus 6* (15%), Candida sepsis 3(7.5%).(Table-7).

Table 7- Outcome Of Sepsis With Different Organisms Isolated.

Organisms	DEATH (n=40)
Klebsiella	24(60%)
MRSA	06(15%)
Pseudomonas	05(13%)
Candida Sep	03(7.5%)
Escherichia Coli	02(5%)

DISCUSSION

Neonatal Septicemia requires rapid approach along with prompt treatment for intact survival and normal neurodevelopment outcome. One of the most common hematological manifestations seen during neonatal sepsis is thrombocytopenia, thus low platelet count may act as an early predictor for the diagnosis of septicemia in neonates.[5]

Out of 1250 admissions in NICU during the study period, 180 neonates had culture positive sepsis. Out of these 180 neonates enrolled, 43% were females and 57% were males which are similar in comparison to study by Heena et al (63.4%) and Pramila et al (58.6%).[6,7]

Present study shows that percentage of thrombocytopenia in neonates admitted with sepsis was high (81%). Severe thrombocytopenia was seen in 16% neonates with sepsis followed by moderate thrombocytopenia (37%), mild thrombocytopenia (28%) and normal platelet count (19%). This indicates that the thrombocytopenia in neonates is having an important correlation with sepsis and admission in the neonatal intensive care unit.[8]

Baseline Characteristics of 180 neonates enrolled in the study showed no statistically significant difference among the study groups. 40% newborns were having normal birth weight, 28% were having low birth weight, 22% were having very low birth weight and 10% were extremely low birth weight. Heena et al observed that low birth weight (76.20%) newborns were high.[6] Vikram et al stated similar finding in their research data.[9] In this study, 68% neonates were appropriate for gestational age, 25% neonates small for gestational age and 7% neonates large for gestational age which was similar to Pramila et al study.[7]

Most commonly, it is the gram negative organisms responsible for neonatal sepsis in developing countries.[8]

In our study, 54% cases are due to gram negative organisms followed by 40% gram positive organisms and 6% fungal sepsis. Among 54% gram negative organisms isolated, *Klebsiella pneumonia* was seen in 56%, *Pseudomonas* 14%, E. coli 12% and *Acinetobacter* 10%. Among 40% gram positive organisms, MRSA was the commonest 53% followed by *Enterococcus* 23% and Coagulase negative *staphylococci* 13%. Among 6% Fungal Sepsis, C*andida sp.* 100% isolated. Rehman et al., reported gram negative organisms as the commonest cause of neonatal sepsis with *E.coli* (36%) accounting for most of cases.[10] Khassawneh et al., from Jordan also reported gram negative organisms as the commonest cause of neonatal sepsis.[11]

"NNPD study" observed that *Klebsiella pneumoniae* (32.5%) was most common isolated organism followed by *Staphylococcus aureus (*13.6%) and *Escherichia coli* (10.6%).[12] Heena et al study also found that *Klebsiella* (54%) was commonest, followed by *Pseudomonas* (15.9%) and *Escherichia coli* (11.1%).[6] It is also similar to Charoo et al, Parvez et al and Swarnkar et al study, where *Klebsiella pneumoniae (48.1%)* was commonest organism followed by *Pseudomonas spp (18.5%)* and *Acetobacter* (14.8%).[13,14,15.]

On the contrary study by Torkman et al, stated that *Enterobacter spp* (39.6%) was the commonest organism and Tripti et al, study showed *Pseudomonas spp*(40%) was the commonest pathogen.[16,17] A study by Kathleen et al found *Group-B Streptococci* (59.8%) was the commonest organism followed by E-coli (40.2%).[18] Pramila et al were also found *Staph. aureus* (58.62%) was the most common followed by *Klebsiella* (16.09%) coagulase negative *Staphylococcus* (6.89%).[7]

In this study, MRSA was the second most common organism responsible for 21% of all cases. Rehman et al., and Kurein et al., also reported 29% and 13% cases of *Staphylococcus aureus* responsible for neonatal sepsis respectively.[10,19.]

Venkateshan S et al., had reported 5-6% incidence of CONS in neonatal sepsis.[20] In developed countries CONS is the major causative organism of late onset sepsis. Sanghvi K P et al., had reported CONS in 61% cases of neonatal sepsis. CONS were isolated less commonly in this study (5%).[21]

In this study, other than bacterial pathogens, fungal organism isolated were 6 % (*Candida spp*), similar to Pramila et al., (2.29%).[7] Venkateshan S et al., and Guida et al., had reported 11% and 8% of fungal sepsis in their respective studies.[20,22] In recent study (2009) by Bhat et al., reported that 8.5% of septic VLBW neonates were having fungal sepsis.[23] Calveros T et al., in 2007, have reported incidence of fungal sepsis in 1% of VLBW neonates.[24]

In this study, severe thrombocytopenia was seen in 16% neonates followed by moderate thrombocytopenia in 37% neonates and mild thrombocytopenia in 28% neonates and normal platelet count in 19% neonates. Vikram R et al in their study reported severe (15%) and moderate thrombocytopenia (15%) respectively among septicaemic newborns which was similar to present study.[9]

Guida et al., in 2003 reported significantly low platelet count at onset of sepsis in gram negative and fungal sepsis.[22] Akarsu et al., had shown lowest platelet count in gram negative than in gram positive sepsis.[25] In this study, mean platelet count at onset of sepsis was lowest in fungal sepsis and gram negative sepsis than in gram positive sepsis which was statistically significant. (P<0.001)

Guida et al., reported low platelet nadir in gram negative and fungal sepsis.[22] Akarsu et al., also reported lowest platelet count in gram negative sepsis than in gram positive sepsis.[25] Bhat et al., had reported significantly low platelet nadir in gram negative and fungal sepsis than gram positive sepsis which was similar to our study (statistically significant P<0.001).[23]

The mean duration of thrombocytopenia was 3.7 days in gram positive sepsis, 7.8 days in gram negative sepsis and 6.5 days in fungal sepsis. The difference between the groups was (p=<0.001). Similar findings were reported by Bhat et al., in their study the average duration of thrombocytopenia was 2.5 days in gram positive sepsis and 8.3 days in gram negative and fungal sepsis (statistically significant).[23] Guida et al., had reported the mean duration of thrombocytopenia of 0.4 days in gram positive sepsis and 2 days in gram negative and fungal sepsis.[22] The greater duration in gram negative sepsis may be attributed to the fact that gram negative sepsis causes severe thrombocytopenia.[26]

In this study it was observed that among 16% severe thrombocytopenic neonates, *Klebsiella pneumoniae (*48%) were commonest organism, followed by *Pseudomonas sp.(*21%) and *Staph. Aureus* (7%). It is comparable to the study by Charoo et al in which they found that severe thrombocytopenia was 60% among *Klebsiella pneumoniae*.[13] Similar observations were also reported by Vikram et al and Arif SH et al.[9,27]

Fungal organism was isolated in 10% of severe thrombocytopenic newborns in this study, contradictory to Sartaj et al study, having 60% association with fungal pathogens and Parvez et al study found 33.3% association with severe thrombocytopenia.[14,28]

Mortality in neonates admitted with sepsis in our study was 22%. Our centre is the tertiary referral centre in north Karnataka with higher rates of complicate deliveries and admissions, which substantiates the higher mortality rate. Among gram negative sepsis, mortality was 32% while gram positive sepsis had 8% mortality and fungal sepsis had 30% mortality. (P<0. 001) Study by Khassawneh et al., and Akarsu et al., had found similar high mortality in gram negative sepsis.[11,25]

Venkateshan S et al., had documented 42% mortality in neonatal sepsis in 1996 which gradually decreased to 20% in 2006.[20] *Klebsiella pneumoniae* 60% was the leading cause of death in the neonates with sepsis followed by *Pseudomonas spp*. 13%, *Staph. aureus* 15%, Candida sepsis 7.5%, *E- coli* 5%. Vergnano et al also attributes *Klebsiella* and *Pseudomonas* to high case fatality rates in his study.[29]

CONCLUSION

Neonatal sepsis contributes to leading cause of mortality in neonates admitted in NICU. Major cause of mortality was by Gram Negative sepsis followed by Fungal and Gram Positive sepsis. Proportion of thrombocytopenia in neonates admitted with sepsis was high. Severe thrombocytopenia was more prevalent in Gram Negative sepsis followed by Fungal and Gram Positive sepsis. Thus thrombocytopenia can be considered as one of the earliest nonspecific predictor of sepsis in neonates admitted in NICU and also it associates significantly with the outcome of the septic neonates.

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