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Original Research Article

Comparison of outcomes of thrombocytopenic and non-thrombocytopenic culture proven neonatal sepsis

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ABSTRACT

Background: Due to high incidence of sepsis as a main cause of neonatal mortality, early detection and proper treatment are important in reducing neonatal mortality. Thrombocytopenia is a common hematological problem encountered during neonatal period, particularly in neonatal sepsis. This study was done to know the incidence of thrombocytopenia in neonatal sepsis and to compare clinical outcome in patients with thrombocytopenic and non-thrombocytopenic neonatal sepsis.
Methods: This was a prospective study carried out at neonatal intensive care unit of a tertiary care teaching hospital of western Gujarat, India, from October 2018 to August 2020. 2739 neonates were admitted with probable sepsis during study period. 299 neonates with positive blood cultures were recruited for the study. They were divided into two groups; group-1 had patients with thrombocytopenia, while group-2 included patients without thrombocytopenia. Severity of thrombocytopenia was assessed in group-1. Micro-organisms isolated and outcome of sepsis were compared in both the groups.
Results: There were 208 neonates in group-1 (thrombocytopenic) and 91 in group-2 (non-thrombocytopenic). There was no significant difference in demographic profiles of neonates in both groups. *Klebsiella pneumonia* was the most common organism isolated from 79 patients of group-1 and 19 patients of group-2 (p=0.033). Coagulase negative *Staphylococci* and *Candida* were the second and third most common micro-organisms isolated from 30.2% and 15.1% of blood cultures respectively. In group-1, 85 (40.8%), 72 (34.6%) and 51 (24.5%) neonates had severe, moderate and mild thrombocytopenia respectively. *Klebsiella pneumoniae* (45.9%) was the commonest organism isolated in severe thrombocytopenic neonates, followed by *Candia* (22.4%) and *Enterococcus* (14.1%).
Conclusions: Thrombocytopenia is a specific marker of neonatal sepsis. The platelet count is a simple test that facilitates diagnostic orientation and the establishment of an early empirical treatment. *Klebsiella pneumoniae* was the commonest organism isolated in severe thrombocytopenic neonates.

Keywords: Micro-organisms, Neonatal sepsis, Thrombocytopenia

INTRODUCTION

Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteremia in the first month of life.[1] It is one of the commonest causes of neonatal mortality contributing to 19% of neonatal deaths.[2] The global burden of neonatal death is estimated to be 5 million of which 3.2 million deaths occur during the first week of life. One fourth of the burden of neonatal mortality worldwide is seen in India and about 1.2 million neonates die every year. Neonatal mortality rate in India as per

2018 data was 23 per 1000 while in Gujarat as per 2017 data it was 21 per 1000 live birth.[3,4]

Thrombocytopenia is a common haematological problem encountered in the neonatal sepsis. Most of the sick, low birth weight and premature infants have low platelet count.[5] Low platelets is usually seen even before the pathogens are cultured from the blood.[6] Platelet count can be considered as one of the parameters useful in early diagnosis of sepsis in symptomatic infants.[7,8]

Gram negative micro-organisms neonatal sepsis are commonly reported from India.[7] Bacteria or bacterial products may cause endothelial damage leading to platelet adhesion and aggregation or may bind directly to the platelet leading to aggregation and accelerated clearance from circulation.[9,10] There may be possibility of immune mechanism for development of thrombocytopenia in septicaemia as there is presence of circulating immune complexes in septicaemia patients and reduced number of complement complex in patients with septicaemic shock.[11,12] Hence, this study was done to know the incidence of thrombocytopenia in neonatal sepsis and to compare clinical outcome in patients with thrombocytopenic and non-thrombocytopenic neonatal sepsis.

METHODS

This prospective comparative study was conducted at NICU of a tertiary care teaching hospital of Western Gujarat, India, from October 2018 to August 2020. During the study period, total 2739 neonates were admitted in our NICU, out of which 299 neonates, with blood culture positive neonatal sepsis, were included in the study. Written informed consents were obtained from parents.

Detailed antenatal history including history of antenatal risk factors for sepsis; such as prolonged rupture of membrane >24 hours prior to delivery (PROM), foul smelling liquor, maternal fever within 2 weeks of delivery or during labor, prolonged labor and >3 sterile or single unclean per vaginal examination, were noted.[13] Detailed natal and postnatal history were also noted. Detailed physical examination was done in all neonates. Demographic profile, type of sepsis (early/late onset sepsis) and presentation (non-specific/systemic) were noted. Sepsis screening tests included estimation of C-reactive protein (>1 mg/dl), total leukocyte count (<5000/mm^3 or >25000/mm^3), micro-ESR (> 15 mm in first hour), low absolute neutrophil counts (as per Manroe chart for term and Mouzinho's chart for very low birth weight neonates) and immature/total neutrophil ratio >0.2.[14-17]

Platelet counts were measured. A normal platelet count ranges from 1,50,000 to 4,50,000 platelets per microliter of blood. Mild, moderate, severe and very severe thrombocytopenia were defined as platelets counts between 1,00,000-1,50,000/mm^3, 50,000-1,00,000/mm^3, 20,000-50,000/mm^3 and <20,000/mm^3 respectively.[18] Confirmation of sepsis was done by blood culture and sensitivity. Blood sample collection was done under full aseptic precautions to avoid contamination. One ml of blood was taken from fresh venipuncture site for blood culture in a bottle containing 5-10 ml of culture media. All samples were incubated at 37 degree celsius and observed for 72 hours for growth of micro-organisms. Reporting of micro-organism growth and antibiotic sensitivity was done as per CLSI guidelines.[19] Lumbar puncture for cerebrospinal fluid examination was done prior to starting antibiotics.[20]

On the basis of platelet counts, all neonates with culture proven sepsis were divided into two groups. Patients with platelet counts <1,50,000/mm^3 were included in group-1 (thrombocytopenic) while patients with platelet counts >150,000/mm^3 were included in group-2 (non-thrombocytopenic).

Statistical analysis was done using Chi-Square test for categorical variables and independent one tailed t-test for continuous variables. Significance was defined as $p<0.05$.

RESULTS

During the duration of this study, 2739 neonates were admitted in our NICU, out of which 299 neonates had blood culture positive neonatal sepsis (CPNS). There were 208 neonates in group-1 (thrombocytopenic) and 91 in group-2 (non-thrombocytopenic). The demographic details of the neonates are shown in (Table 1). The mean birth weight of neonates in groups 1 and 2 were 2.39 kg ($\pm$0.834) and 1.75 kg ($\pm$0.353) respectively (p=0.331). Among 299 neonates, 173 (57.8%) were males, of which 71.7% (124/173) were in group-1 and 28.3% (49/173) were in group-2 (p=0.628). Total female neonates were 126 (42.2%); out of which 66.7% (84/126) were in group-1 and 33.3% (42/126) were in group-2 (p=0.556). Total preterm neonates were 105 (35.1%); out of which 62.8% (66/105) were in group-1 and 37.2% (39/105) were in group-2 (p=0.205). Total full-term neonates were 194 (64.9%); out of which 73.2% (142/194) were in group-1 and 26.8% (52/194) were in group-2 (p=0.385). Total 257 (86.3%) neonates had early onset sepsis (EOS); out of which 70.4% (181/257) were in group-1 and 29.6% (76/257) were in group-2 (p=0.824). Late onset sepsis (LOS) was present in 42 (13.7%) neonates; out of which 64.3% (27/42) were in group-1 and 35.7% (15/42) were in group-2 (p=0.488). Out of 299 neonates, 187 (62.5%) neonates were born by normal vaginal delivery (NVD); out of which 69% (129/187) were in group-1 and 31% (58/187) were in group-2 (p=0.892). Total 112 (37.5%) neonates were delivered by cesarian section (LSCS); among them 70.5% (79/112) were in group-1 and 29.5% (33/112) were in group-2 (p=0.848) (Table 1). *Klebsiella pneumonia* was the most common organism isolated in 98 (32.7%) blood cultures; out of which 79

(80.6%) were isolated from group-1 while only 19 (19.4%) were isolated from group-2 (p=0.033).

Coagulase negative staphylococci (CoNS) was the second most common organism isolated in 90 (30.2%) blood cultures; out of which 51 (56.7%) were isolated from group-1 and 39 (43.3%) were in group-2 (p=0.022). Candida was third most common organism found in 45 (15.1%) blood cultures; out of which 37 (82.2%) were isolated from group-1 and 8 (17.8%) were isolated from group-2 (p=0.080).

Less common micro-organisms isolated were *Enterococcus* (11.1%), *Staphylococcus aureus* (5.6%), *Escherichia coli* (2.3%), *Acinetobacter* (2%) and *Pseudomonas* (1%) (Table 2).

Table 1: Demographic profiles of neonates with culture proven neonatal sepsis.

Parameters	Thrombocytopenic (group-1) N (%)	Nonthrombocytopenic (group-2) N (%)	P value
Birth weight (Kg)*	2.39±0.834	1.75±0.353	0.331
Male (N=173)	124 (71.7)	49 (28.3)	0.628
Female (N=126)	84 (66.7)	42 (33.3)	0.556
Preterm (N=105)	66 (62.8)	39 (37.2)	0.205
Term (N=194)	142 (73.2)	52 (26.8)	0.385
EOS (N=257)	181 (70.4)	76 (29.6)	0.824
LOS (N=42)	27 (64.3)	15 (35.7)	0.488
NVD (N=187)	129 (69)	58 (31)	0.892
LSCS (N=112)	79 (70.5)	33 (29.5)	0.848

*Values in mean±SD.

Table 2: Microorganism isolated from blood cultures.

Micro-organism	Thrombocytopenic (group-1) N (%)	Nonthrombocytopenic (group-2) N (%)	P value
***Klebsiella pneumonia* (N=98)**	79 (80.6)	19 (19.4)	0.033
CoNS (N=90)	51 (56.7)	39 (43.3)	0.022
***Candida* (N=45)**	37 (82.2)	8 (17.8)	0.080
***Enterococcus* (N=33)**	22 (66.7)	11(33.3)	0.731
***Staphylococcus aureus* (N=17)**	8 (47)	9 (53)	0.052
***Escherichia coli* (N=7)**	4 (57.1)	3 (42.9)	0.481
***Acinetobacter* (N=6)**	5 (83.3)	1 (16.6)	0.466
***Pseudomonas* (N=3)**	2 (66.7)	1 (33.3)	0.913

Table 3: Severity of thrombocytopenia and the micro-organisms isolated.

Micro-organism	Mild thrombocytopenia (N=51), frequency (%)	Moderate thrombocytopenia (N=72), frequency (%)	Severe thrombocytopenia (N=85), frequency (%)
Klebsiella pneumoniae	12 (23.5)	28 (38.9)	39 (45.9)
CoNS	19 (37.2)	22 (30.6)	10 (11.8)
Candida	7 (13.7)	11 (15.2)	19 (22.4)
Enterococcus	5 (9.8)	5 (6.9)	12 (14.1)
Staphylococcus aureus	4 (7.8)	3 (4.2)	1 (1.2)
Escherichia coli	1 (2)	1 (1.4)	2 (2.2)
Acinetobacter	2 (4)	2 (2.8)	1 (1.2)
Pseudomonas	1 (2)	0 (0)	1 (1.2)

In group-1, 85 (40.8%), 72 (34.6%) and 51 (24.5%) neonates had severe, moderate and mild thrombocytopenia, respectively. *Klebsiella pneumoniae* 45.9% (39/85) was the commonest organism isolated in severe thrombocytopenic neonates, followed by Candida 22.4% (19/85) and *Enterococcus* 14.1% (12/85) (Table 3). Out of 299 culture proven neonatal sepsis, 67 (22.4%) neonates expired and 232 (77.6%) neonates were discharged. Out of 232 neonates, 158 (75.96%) and 74 (81.3%) neonates were successfully discharged from group-1 and 2 respectively (p=0.718). Out of 67 neonates that expired, 50 (24%) and 17 (18.6%) neonates were from group 1 and 2 respectively (p=0.411) (Table 4).

Table 4: Outcome of neonatal sepsis in thrombocytopenic and non-thrombocytopenic groups.

	Thrombocytopenic (group-1), N (%)		Nonthrombocytopenic (group-2), N (%)	P value
Discharged (N=232)	158 (75.9)		74 (81.3)	0.718
Expired (N=67)	Severe thrombocytopenic	26 (12.5)	17 (18.6)	0.411
	Moderate thrombocytopenic	12 (5.8)		
	Mild thrombocytopenic	12 (5.8)		

DISCUSSION

In current study, incidence of sepsis was 10.9%, as 299 out of 2739 admitted neonates in our NICU had blood culture proven sepsis. In a study by Ree et al, 460 of 6551 (7%) neonates had sepsis.[21] In current study, *Klebsiella pneumonia* was more commonly isolated in patients with thrombocytopenia that who were non-thrombocytopenic. Ree et al also found than gram negative sepsis is more commonly associated with thrombocytopenia (15%) as compared to non-thrombocytopenia (6%) (p=0.004).[21] Heena et al, also found *Klebsiella pneumoniae* in 54% neonates with sepsis.[22]

In current study 67.2% neonates with CPNS had thrombocytopenia. This indicates that the low platelets count in newborns has an important correlation with sepsis. The incidence of thrombocytopenia in our study is comparable with other studies conducted by Ree et al (49%), Goudar et al (59%) and Charoo et al (59.5%).[21,23,24] In current study, severe thrombocytopenia was found in 40.8% neonates, followed by moderate (34.6%) and mild (24.5%) thrombocytopenia. Singh et al observed that severe, moderate and mild thrombocytopenia were present in 36.2%, 34.2% and 24.8% neonates respectively, which is comparable to our study.[25] Ree et al and Goudar et al found severe thrombocytopenia in 20% and 15% neonates with CPNS respectively, which is low as compared to our study.[21,23] In our study, we found that *Klebsiella pneumoniae* was the most common organism associated with thrombocytopenia (37.9%) and also with severe thrombocytopenia (45.9%). Among all the organisms responsible for thrombocytopenia, *Pseudomonas* was the least common organism (0.01%). Charoo et al and Arif et al also found *Klebsiella pneumoniae* as the most common organism associated with thrombocytopenia in 58% and 73.3% neonates respectively.[24,26] In current study, there was no significant difference in mortality rates (p=0.411) between non-thrombocytopenic and thrombocytopenic neonates.

CONCLUSION

It was observed that 69.3% neonates with culture proven neonatal sepsis had thrombocytopenia. So, thrombocytopenia is specific marker of neonatal sepsis. The platelet count is a simple test that facilitates diagnostic orientation and the establishment of an early empirical treatment for neonatal sepsis. In our study, *Klebsiella pneumoniae* was the commonest organism isolated in severe thrombocytopenic neonates. So, whenever a neonate has thrombocytopenia with sepsis, effective antibiotics against *Klebsiella pneumoniae* should be started till confirmed culture report is obtained.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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