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Association of thrombocytopenia with specific organism and mortality in neonatal sepsis

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Abstract

Introduction: Neonatal sepsis is one of the leading causes of mortality worldwide. Knowing the association of thrombocytopenia to the specific organism can help to choose the correct antibiotic before a culture sensitivity report becomes available. Hence, this study was planned to find out if thrombocytopenia is associated with any specific type of organism in neonatal sepsis and higher mortality.

Method: It was a retrospective observational study done at the neonatal intensive care unit at Patan Hospital. The samples were taken over three years, from April 2018 to March 2021. All culture-positive sepsis within the study period were included. The cases whose files were missing were excluded. Neonatal sepsis was defined as cases where a blood culture was positive for the organism. The data was analyzed using SPSS 16.

Result: There were 51 cases whose analysis was done. Klebsiella 25(49.02%) and Acinetobacter 11(21.57%) were the most common organisms. Fifty-nine percent of cases had thrombocytopenia among which 5(10%), 6(12%), and 19(37%) had mild, moderate, and severe thrombocytopenia, respectively. Klebsiella sepsis was significantly associated with thrombocytopenia (p-value 0.001). The sensitivity of Klebsiella to Meropenem and Colistin was 70% and 100% respectively. Mortality was not associated with thrombocytopenia.

Conclusion: In the study, thrombocytopenia was associated with Klebsiella sepsis in neonates. Hence, in thrombocytopenic patients with clinical suspicion of sepsis, proper antibiotics to cover Klebsiella should be started empirically till a blood culture report becomes available.

Keywords: mortality, neonatal sepsis, thrombocytopenia

Introduction

Neonatal sepsis is one of the leading causes of mortality worldwide.[1] The definite diagnosis of neonatal sepsis is established when blood culture is positive. The worldwide incidence of neonatal sepsis is 2824 per hundred thousand live births with a mortality of 17.6 percent.[1] In South Asia, hospital-based reports show the incidence of neonatal sepsis to be 15.8 per thousand live births with a median case fatality rate of 34.4 percent.[2] In Nepal, hospital based studies have shown to have culture-positive sepsis in 14 to 20 percent.[3,4] Group B streptococcus and E. coli are the leading cause of neonatal sepsis worldwide but different studies have shown different organisms to be the common pathogens.[4,5]

Though there are many non-infective causes of thrombocytopenia in neonates, sepsis is an important and common cause. Some studies have shown that thrombocytopenia is associated with higher mortality in neonatal sepsis.[6] Few studies suggest thrombocytopenia is associated with gram negative or fungal organisms while other studies show different results.[7,8,9] A study from Nepal shows almost 49 percent of blood culture positive sepsis had thrombocytopenia however association with any specific organism was not studied.[10]

Laboratory report of platelet count is available much earlier than blood culture report. Knowing the association of thrombocytopenia to the specific organism can help to choose the correct antibiotic before a culture sensitivity report is available. Hence, this study was conducted to find out if thrombocytopenia is associated with any specific types of organisms in neonatal sepsis and higher mortality.

Method

A retrospective observational study was done at the neonatal intensive care unit (NICU) of Patan Hospital. The cases were taken over three years from April 2018 to March 2021. The study was conducted after obtaining ethical clearance from the institutional review committee (Ref. no. drs2106181541). All culture positive sepsis within the study period were included. The cases in which platelet count was not sent at the time of sending blood culture and whose files were missing were excluded. Data was collected from neonatal intensive care unit registers, audits, and case files from the medical record section. Data were collected in structured proforma.

Neonatal sepsis was defined as the cases where blood culture was positive for an organism.[11] Neonatal data like gestational age, mode of delivery, birth weight, Apgar score, the need for neonatal resuscitation, and small for gestational age status were taken. Risk factors for sepsis, like vaginal leaking for more than 18 h and maternal fever more than 100.4 ^{0}F within 2 weeks of delivery were recorded.[12] Gestational age was taken from the last menstrual period. Low birth weight was defined as birth weight less than 2500 grams. Small for gestational age was defined as birth weight less than the tenth percentile for the gestational age.[13] Mode of delivery was recorded as vaginal or caesarean delivery. As per the standard practice, complete blood count, C-reactive protein (CRP), and blood culture were sent at the same time while doing septic workup. The blood culture reports showing organisms and their sensitivity patterns were noted. Total count, neutrophil count, platelet count, and CRP sent at the time of sending blood culture were noted. Thrombocytopenia was defined as the platelet count of less than 150,000 cells per mm^3. Mild, moderate, and severe thrombocytopenia were 100,000-150,000 cells per mm^3, 50,000-100,000, and less than 50,000 cells per mm^3 respectively. The outcome of the patient and the length of hospital stay were recorded.

The data was collected in Microsoft Excel and further analyzed using SPSS version 16. Qualitative data were expressed as number and percentage and quantitative data were expressed as mean, median, and standard deviation. Chi-square test or Fisher's exact test was used to see the association between thrombocytopenia and specific organisms, and between thrombocytopenia and mortality.

Result

During the study period, there were 524 patients admitted to NICU, out of which 60(11.45%) were culture positive sepsis. Among them, in 9(15%) cases platelet count was not sent at the time of blood culture and were excluded. Hence final analysis was done among 51(85%) cases. Most of them were preterm, had low birth weight, and were born by cesarean section, Table 1. Gestational age ranged from 25^{+1} w to 40^{+4} w. Among them, 30(58.82%) were males and 21(41.18%) were females. The mean weight of all babies was 1616±680 g with a range of 840 to 4160 g. The mean time of sending the blood culture was 9.22±9.24 d with a range of 1 to 42 d. Among all culture positive cases, early-onset sepsis was 14(27.45%) and late-onset sepsis with onset more than 72 h of life was 37(72.55%). The mean duration of hospital stay was 31.65±26.6 d with a range of 3-102 d.

Among the patients with sepsis, 30(59%) had thrombocytopenia; most of them had severe thrombocytopenia, Figure 1.

The incidence of thrombocytopenia was 31(59%), Table 2. Most of them were gram-negative bacteria. Klebsiella was the most common organism in blood culture. Thrombocytopenia was also most common in babies with Klebsiella sepsis. Among all organisms, only Klebsiella sepsis was significantly associated with thrombocytopenia (p=0.001). Other organisms were not associated with thrombocytopenia.

Four babies (7.84%) expired among all neonatal sepsis out of which only two had thrombocytopenia. Thrombocytopenia was not associated with mortality (p=0.549), Figure 2.

Klebsiella was sensitive to Colistin in all cases. There were almost 30% cases of Meropenem-resistant Klebsiella. Carbapenem-resistant Acinetobacter and Enterobacter were seen in 60% and 70% respectively. Enterobacter and Acinetobacter were more resistant to Meropenem. All the cases of Coagulase-negative staphylococcus (CONS) were Oxacillin resistant but were Vancomycin and Linezolid sensitive, Table 3.

Table 1. Clinicodemographic profile of the neonates with sepsis (N=51)

	Demographic profile	N	%
Demographic	Low birth weight	46	90.20
	Preterm babies	46	90.20
	Small for gestational age	10	19.61
	Vaginal delivery	15	29.41
	Need of neonatal resuscitation	19	37.25
	Apgar score < 7 at 1 minutes	25	49.02
Risk factors	Maternal fever within 2 weeks of delivering	2	3.92
	Per vaginal leaking for more than 18 hours	2	3.92
Investigations	High CRP >10 mg/L	34	66.67
	Leucopenia (leucocyte count less than 5000/mm^3	10	19.61

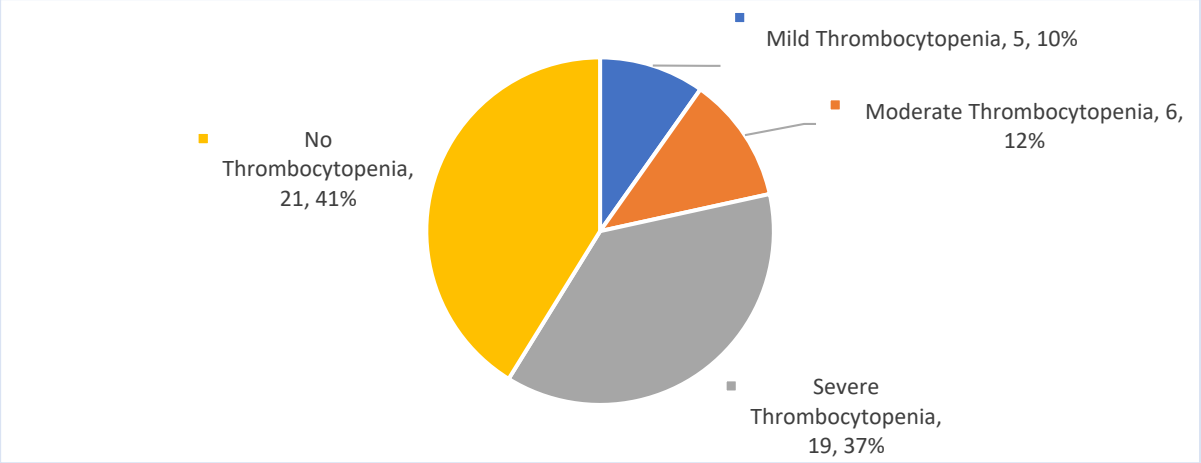

Figure 1. Incidence of thrombocytopenia in sepsis (N=51)

Table 2. Comparison of thrombocytopenia among different organisms causing neonatal sepsis (N=51)

Organism	N (%)	Thrombocytopenia (%)	p-value
Gram Negative	45(88)	28(62.22)	0.182
Klebsiella	25(49.01)	20(80)	0.001
Acinetobacter	11(21.57)	4(36.36)	0.872
Enterobacter	8(15.69)	4(50)	0.43
E. coli	1(1.96)	0(0)	0.412
Gram Positive	6(12)	2(33.33)	0.182
Coagulase negative staphylococcus	5(9.8)	1(20)	0.085
Staphylococcus aureus	1(1.96)	1(100)	0.588

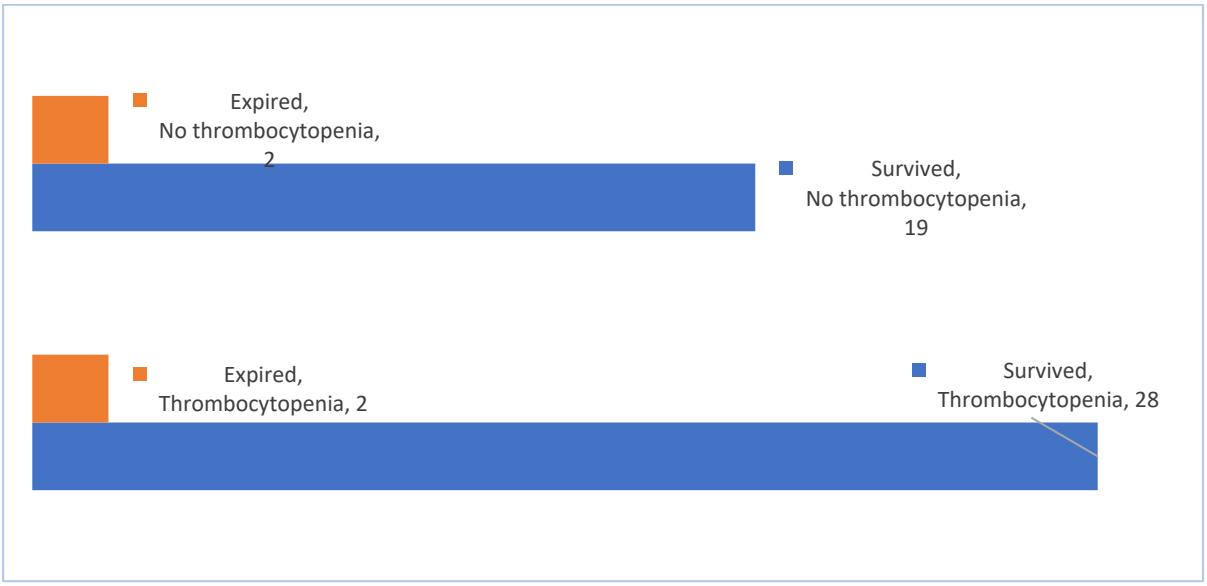

Figure 2. Relation between thrombocytopenia and mortality in neonatal sepsis (N=51)

Table 3. Antibiotic sensitivity pattern of the common pathogens (N=51)

	Klebsiella		Acinetobacter		Enterobacter		CONS	
	R/(R+S)	S%	R/(R+S)	S%	R/(R+S)	S%	R/(R+S)	S%
Ampicillin	23/24	4.2	1/1	0	8/8	0	1/4	75
Cefotaxim	2/7	71.4	-	-	2/2	0	-	-
Pipercillin-Tazobactum	10/21	52.4	6/11	45.5	3/3	0	-	-
Amikacin	6/22	72.7	7/11	36.4	1/7	85.7	1/1	0
Gentamycin	10/24	58.3	8/9	11.1	4/7	42.9	3/4	25
Ofloxacin	6/22	72.7	1/1	0	1/6	83.3	3/4	25
Chloramphenicol	11/22	50	0/1	100	5/6	16.7	-	-
Meropenem	7/24	70.8	6/10	40	2/7	71.4	-	-
Colistin	0/5	100	0/8	100	0/2	100	-	-
Linezolid	-	-	-	-	-	-	0/4	100
Oxacillin	-	-	-	-	-	-	4/4	0
Vancomycin	-	-	-	-	-	-	0/4	100

Discussion

This study shows Klebsiella sepsis was associated with thrombocytopenia but sepsis caused by other organism was not. Thrombocytopenia was not significantly associated with mortality. The most common cause of neonatal sepsis was Klebsiella. Different studies have shown the association of thrombocytopenia with specific organisms. A study from Bangladesh shows the incidence of thrombocytopenia was high among patients who had gram negative sepsis, concurrent bacterial and fungal sepsis (4/4, 100%) and also isolated fungal sepsis (11/11; 100%).[14] A study from Aligarh showed that in gram negative septicemia, thrombocytopenia was more severe as compared to gram positive septicemia.[15] A study from Netherlands showed gram negative sepsis was independently associated with thrombocytopenia as opposed to gram positives in neonatal sepsis.[6] A study from Iran showed a higher incidence of thrombocytopenia with Enterobacter sepsis.[7] However a study from India showed the incidence of thrombocytopenia to be more in gram positive sepsis (15/21,71.41%) than in gram negative sepsis (35/54,64.81%) and fungal sepsis (3/5,60%).[16] This study shows thrombocytopenia to be significantly associated with Klebsiella sepsis only. Less cases of other organisms compared to Klebsiella might be the reason not to have a significant association of other organisms with thrombocytopenia.

In our study, culture positive cases were 60(11.45%) among total admissions. A study from the Netherlands showed culture positivity of 460(7%).[6] Studies from Bhutan and Bangladesh showed a culture positive rate of 44(1.9%) and 104(7.45).[17,18] In Nepal, hospital based studies had shown to have culture positive sepsis in 30(14%) to 69(20%).[3,4,19] Lack of adequately separated area within NICU, need of sharing the equipment among septic and non-septic babies, and need of same person caring septic and non-septic babies due to a poor patient-to-staff ratio are few causes of having high infection rates in resource-poor settings.

Thrombocytopenia was found in 30(60%) cases of neonatal sepsis while severe thrombocytopenia was seen in 19(37%) in this study. A study from Bangladesh showed 67.8% of babies with sepsis had thrombocytopenia.[14] Another study from Kashmir showed thrombocytopenia in 119(59.5%) of culture positive sepsis among them 54(27%) of babies had mild thrombocytopenia, 40(20%) had moderate thrombocytopenia and 25(12.5%) had severe thrombocytopenia among 200 babies.[20] A study in India showed an incidence of thrombocytopenia in gram negative and positive sepsis to be 35(64.81%) and 15(71.41%) respectively.[16] Another study showed severe thrombocytopenia occurred in 92(20%) of septic neonates.[6] A study from Pakistan showed thrombocytopenia had sensitivity, specificity, positive predictive value, negative predictive value 64.3, 90, 64.3,

and 90 percent respectively to predict neonatal sepsis.[21] So the incidence of thrombocytopenia in our study population was similar to other studies. Thrombocytopenia in neonatal sepsis is mainly due to the increased destruction of platelets. Neonates respond to sepsis by up-regulating thrombopoiesis and thrombocytopenia occurs when the rate of platelet consumption exceeds the rate of platelet production.[22] In severe illness-specific platelet or bacterial products down-regulate the magnitude of the thrombopoietic response and lead to a state of relative hyperproliferation which also contributes to thrombocytopenia.[23]

Klebsiella was the most common organism in the study population followed by Acinetobacter. The majority 37(72.55%) of them were late-onset sepsis likely nosocomial infection. A study from Nepal showed Staphylococcus to be the most common organism 21(35.6%).[19] In the study from Kashmir, Klebsiella was the most common organism 125(62.5%).[20] A study from Bangladesh showed Acinetobacter to be the most common organism 22(25%).[14] While another study from Bangladesh showed E. coli and Klebsiella to be the most common causes.[24] A study in Bhutan showed coagulase negative Staphylococci were the commonest isolate followed by Klebsiella pneumoniae.[17] A study in Iran showed Enterobacter to be the most common organism 21(39.4%).[7] A study from South and North India also showed Staphylococcus to be the most common organism.[25,26] Most of these organisms being nosocomial infections, the difference in the organism may be attributed to the microorganism present in the particular NICU.

Recent studies showed emerging antibiotic resistance among organisms causing neonatal sepsis. In our study, sensitivity of Klebsiella to Meropenem was 17(70.8%). Our study showed 6(60%) resistance of Acinetobacter to Meropenem. Studies from Bangladesh and India showed Meropenem and Imipenem sensitivity of only about 38% and 70(92.1%) to Klebsiella.[27,28] In another study, Acinetobacter was resistant to Imipenem in 7(100%) cases.[27] The study showed 95% resistance of Acinetobacter to Meropenem.[27] Low birth weight and prematurity requiring long NICU stay, need of mechanical ventilation in more cases and use of central catheters are the reasons that the babies in NICU are at more risk of getting sepsis with multidrug-resistant microorganisms. Effective antibiotic stewardship, adequate hand hygiene, judicious use of antibiotics, and cohorting of patients and staff when babies get infected are effective interventions to limit the spread of resistant organisms in the NICU.

The association between thrombocytopenia and mortality in neonates has been demonstrated in different studies. This study failed to show the relationship between thrombocytopenia and mortality. Studies from Netherland and India showed a significant relation between thrombocytopenia and mortality.[6,29] A study showed mortality rate did not correlate with the lowest platelet count but increased with the number of platelet transfusions.[30] Small sample size and lower mortality rate might be the reason that this study failed to show the relationship between thrombocytopenia and mortality.

There are a few limitations of the study. Small sample size is one of them. There are other causes of thrombocytopenia in neonates like maternal preeclampsia, small for gestational age, medications, etc. which were not considered in this study. Thrombocytopenia in culture-positive cases was considered to be due to sepsis. Further studies with a larger sample size are needed to reach a definite conclusion.

Conclusion

In the study, setting thrombocytopenia was associated with Klebsiella sepsis in neonates. Hence in thrombocytopenic patients with clinical suspicion of sepsis, proper antibiotics to cover Klebsiella should be started empirically till a blood culture report becomes available. The choice of empirical antibiotic should be started depending on the local antibiotic sensitivity pattern.

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Author Contribution
Concept, design, planning: ALL (SC, SM, PK, DS, AS); Literature review: SC, SM, PK, AS; Data collection: ALL; Data analysis: ALL; Draft manuscript: SC, SM, PK, AS; Revision of draft: ALL; Final manuscript: ALL; Accountability of the work: ALL.

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