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Original Research Article

A Hospital Based Prospective Observational Cross-Sectional Study to Assess the Thrombocytopenia and Variations in Platelet Indices in Neonatal Sepsis

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Abstract

Aim: The present study was undertaken to evaluate thrombocytopenia and variations in platelet indices in neonatal sepsis.

Methods: This hospital based prospective observational cross-sectional study was conducted in Department of Pathology, SKMCH, Muzaffarpur, Bihar, India over a period of 12 months. A total of 200 Neonates under the age of 28 days admitted in NICU, were studied and 100 at risk neonates' were detected and included in our study.

Results: Most common presentation in EOS is respiratory distress, and in LOS is refusal of feeds, and overall common presentation is refusal of feeds. Total 200 neonates were examined. 100 neonates (50%) were at risk. 12 (12%) were had no sepsis (NOS), 40 (40%) were Early onset sepsis (EOS) and 48 (48%) were Late onset sepsis (LOS). In EOS, thrombocytopenia was found in 80%, whereas it was 83.34% in LOS. It was seen that thrombocytopenia was the most sensitive marker (83.08%) followed by MPV and PDW in detecting neonates with culture‑positive sepsis. However, it has a low specificity (20.33%). But when we combine MPV and PDW or combined all the three markers (MPV + PDW + PC), the specificity increased to 46.34%.

Conclusion: NNT can be used as screening tool in NNS as it is easy and cost-effective. It requires further large scale studies and meta-analysis to validate. Mortality in sepsis cases increases with severity of thrombocytopenia.

Keywords: Thrombocytopenia, Neonatal, Sepsis, Platelet Indices.

Introduction:

Neonatal sepsis causes significant mortality and long term morbidity in neonates, especially for preterm infants of very low birth weight. [1-3] In 2015, 2.7 million deaths, or roughly 45% of all under-five deaths, occurred during first 28 days of life. [4] More than one-third of the estimated 4 million neonatal deaths around the world each year are caused by severe infections and a quarter (around one million deaths) are due to neonatal sepsis/ pneumonia alone. [5]

Sepsis is a non-specific inflammatory defence mechanism and is considered a generalized process where every organ and system can be involved. The haemostatic

system is frequently disturbed during sepsis. Haematological changes induced in neonatal sepsis have been used to make an early diagnosis and to detect complications. Changes in platelet count and platelet indices such as mean platelet volume (MPV) and platelet distribution width (PDW) induced by neonatal sepsis have been the focus of various studies. Changes in Platelet parameters like MPV and PDW are helpful in diagnosis of neonatal sepsis but these indices have not been extensively studied in neonatal sepsis.

Thrombocytopenia is one of the early but non-specific indicator of neonatal sepsis. [6] It can be caused by bacterial, viral, fungal and parasitic infections and other non-infectious causes. [7] Bleeding is a major complication of thrombocytopenia but is generally limited to infants with count < 30000/mm^3. [8,9] Studies have shown that approximately 50% cases of culture-proven sepsis have thrombocytopenia. [10,11] However, it is a diagnostic challenge as there are overlapping signs and symptoms which preclude a specific diagnosis of sepsis. A high index of suspicion and its confirmation are necessary for the early diagnosis of sepsis. Various tests are traditionally applied. [12] Although blood culture is a gold standard for diagnosis, it is not without limitations. Supreetha et al. reported that a definite diagnosis of septicemia by a positive blood culture required a minimum period of 48–72 h and yielded a positive result in 30%–70% of cases. [13] The negative predictive value (NPV) of various sepsis screen parameters is too low to confidently rule out sepsis.

Hence the present study was undertaken to evaluate thrombocytopenia and variations in platelet indices in neonatal sepsis.

Methods

This hospital based prospective observational cross sectional study was conducted in De sab mil SKMCH, Muzaffarpur, Bihar, India over a period of 12 months. A total of 200 Neonates under the age of 28 days admitted in NICU, were studied and 100 at risk neonates' were detected and included in our study.

Investigations done – sepsis screening

Total Leukocyte Count (TLC): <5000/cmm or >15,000/cmm.

Absolute Neutrophil Count (ANC): <1800/cmm

Immature to Total Neutrophil (I/T) RATIO: >0.2 (immature neutrophils / ANC), highly sensitive of NNS, I/T = (Immature neutrophils like band forms, metamyelocytes, myelocytes) /Mature + immature neutrophils CRP:>1mg/dL MICRO ESR (u-ESR):> (age in DOL +3)mm or >15 mm/1st hr, specific but moderate sensitivity.

IL- 6, and Procalcitonin were not included due to practical problems.

Blood culture and Chest Xray

NOTE: (≥ 2) positive screening parameters (TLC,ANC,I/T ratio, CRP, u-ESR) taken as sepsis screen positive (Sn 93%,PPV 39%, >2 parameters – NPV 99%)and that neonate is with sepsis.

Exclusion criteria

Mother with History s/o ITP, SLE / other autoimmune disorders, on medication during pregnancy (sulfonamides, quinine / quinidine) (thiazides, tolbutamide, vancomycin, hydralazine, and heparin).

Neonate with h.s/o bleeding disorder in family, trisomies, Turner /Noonans syndromes, TAR syndrome.

Conditions associated with sequestration of platelets (Kasabach - merritt syndrome with giant haemangiomas, renal veinthrombosis, polycythemia, CCHD, placental vascular thrombi – PIH /preeclampsia /eclampsia). Severe Rh – HDN (marked erythropoiesis in bone marrow → neutropenia and thrombocytopenia)

Massive bleed from causes like birth trauma, accidental slipping of cord clamp causing hemodynamic disturbance/ exchange transfusion (dilutional NNT). Sick neonate with RVT, CHD, Congenital leukemia. Neonate who received IV antibiotics for ≥ 48 hrs prior to our study.

All neonates enrolled were investigated for blood culture, sepsis screen [C‑reactive protein (CRP), total leukocyte count (TLC), absolute neutrophil count (ANC), immature to total neutrophil (IT) ratio], and platelet indices (platelet count, MPV, PDW). For this, approximately 2 mL of venous blood was drawn from each neonate through peripheral veins.

Statistical Analysis

Microsoft Office 2007 was used for the analysis of results. Descriptive statistics like mean and percentages were used for interpretation of results.

Results

Table1: Clinical presentation in NNS

Clinical presentation	EOS	LOS	NOS	Total
Maternal fever	2	1	1	4
PROM	3	1	1	5
Foul smelling liquor	1	-	-	1
Refusal of feed	6	15	4	25
Respiratory Distress	16	3	1	20
Lethargy	2	11	1	14
MAS / BA	8	3	1	12
Convulsions	6	10	-	10
Repeated vaginal examinations	1	1	1	3
Poor hygiene	1	1	0	2
Top / pre-lacteal feeds	2	1	2	4

Most common presentation in EOS is respiratory distress, and in LOS is refusal of feeds, and over all common presentation is refusal of feeds.

Table 2: Thrombocytopenia in neonatal SEPSIS

	With NNT	Without NNT	Total
EOS	32 (80%)	8 (20%)	40
LOS	40 (83.34%)	8 (16.66%)	48
NOS	5 (41.66%)	7 (58.34%)	12
Total	77	23	100

Total 200 neonates were examined. 100 neonates (50%) were at risk. 12 (12%) were had no sepsis (NOS), 40 (40%) were Early onset sepsis (EOS) and 48 (48%) were Late onset sepsis (LOS). In EOS, thrombocytopenia was found in 80%, whereas it was 83.34% in LOS.

Table 3: Platelet count distribution in NNT

Platelet count	EOS	LOS	NOS	Total
< 0.5 lakhs / mm3	10	13	2	25 (32.46%)
0.5 – 1 lakhs / mm3	7	10	1	18 (23.37%)
1 – 1.5 lakhs / mm3	15	16	3	34 (44.15%)
Total	32	38	7	77 (100%)

Most of the NNT were with platelet count between 1 to 1.5 lakhs (44.15% of total NNT).

Table 4: NNT distribution in NNS

Test (NNT)	Diagnosis (DISEASE – Sepsis)		Total
	NNS +VE	NNS -VE	
NNT +VE	(a) True Positive: 74	(b) False Positive: 3	77
NNT -VE	(c) False negative: 15	(d) True Negative: 8	23
Total	89	11	100

There were 77 neonates in NNT +ve in the study and 23 neonates in NNT –ve.

Table 5: Performance Variables of Platelet Indices for Diagnosis of Neonatal Sepsis with Blood Culture Being Gold Standard

	Sensitivity	Specificity	PPV	NPV
Platelet count <1.5 lakhs/mm3	83.08	20.33	35.53	69.44
MPV >10.8 fl	78.46	33.33	38.35	74.55
PDW >19.1 fl	72.31	35.77	37.30	70.97
Platelet count + MPV + PDW	63.08	46.34	38.32	70.37
Platelet count + MPV	69.23	34.96	36.00	68.25
Platelet count + PDW	69.23	37.40	36.89	65.15
MPV + PDW	64.62	46.34	38.89	71.25

The sensitivity and specificity of platelet indices for diagnosis of neonatal sepsis were assessed by comparing them against blood culture which is the gold standard for diagnosis of neonatal sepsis. It was seen that thrombocytopenia was the most sensitive marker (83.08%) followed by MPV and PDW in detecting neonates with culture‑positive sepsis. However, it has a low specificity (20.33%). But when we combine MPV and PDW or combined all the three markers (MPV + PDW + PC), the specificity increased to 46.34%.

Table 5: Correlation between Markers of Platelet Indices with Positive Sepsis Screen and Gold Standard Blood Culture

	Sensitivity	Specificity	PPV	NPV
Sepsis screen + platelet count	50.77	44.72	32.67	63.22
Sepsis screen + MPV	50.77	52.03	35.87	66.67
Sepsis screen+PDW	44.62	55.28	34.52	65.38
Sepsis screen + platelet count + MPV + PDW	40.00	62.60	36.11	66.38
Sepsis screen + Platelet count + MPV	43.08	53.66	32.94	64.08
Sepsis screen + platelet count + PDW	43.08	56.10	34.15	65.09
Sepsis screen + MPV + PDW	41.54	62.60	36.99	66.96

The sensitivity of sepsis screen in this study was 60% (which was lower than the sensitivity of platelet indices) and specificity was 31.71%. However, when we combine sepsis screen and platelet indices, the specificity for diagnosis of neonatal sepsis increased to 62.6% in our group of neonates.

Discussion

Neonatal sepsis is a life threatening condition which needs urgent diagnosis and proper management. The early signs and symptoms of sepsis in the newborn are nonspecific and subtle and might be easily confused with other non-infectious causes. A definitive diagnosis of neonatal sepsis can be made only with a positive blood culture. However, it may yield false positive results due to contamination or negative results even with severe infection. The most important approach is early diagnosis and treatment of neonates with

sepsis. Thus there is need for alternative early valid markers of neonatal sepsis.

Guida et al. [11] had reported that 54% septic Very Low Birth Weight (VLBW) neonates developed thrombocytopenia. Khalada Binte Khairand Mohammad Asadur Rahman et al [14], studied 'Role of Hematologic Scoring System in Early Diagnosis of Neonatal Septicaemia' they found that platelet count<1,00,000/mm^3 had a sensitivity of 60%, specificity 82%, PPV 31% and NPV 94%.

In the present study it was found that NNT (< 1,50,000/ mm^3) can be used to screen neonate with sepsis (NNS) with Sensitivity of 77%, and acceptable Specificity, Positive predictive value, especially in ' at risk neonates' which is cost effective and available in almost all hospitals, particularly useful in developing countries like India. In the present study, blood culture positivity was observed in 25 (25%) neonates. Of these 13 were EOS and rest were LOS. Thrombocytopenia was found in 77 septic neonates (77%). These findings indicate that low platelet count is important finding in bacterial septicemia. Further it was also observed that thrombocytopenia was noted in majority of cases in which blood culture was negative.7 Therefore, it was observed from the study that platelet count is an important indicator of septicemia and not related with blood culture, although not specific.

We found significant high prevalence of thrombocytopenia in culture proven neonatal sepsis. Results were statistically significant when compared with culture negative neonatal sepsis (p= 0.003). In studies by Guida et al [11] and Mannan MA et al [15] they observed the prevalence was 50% among babies with culture positive sepsis. Neonatal sepsis is an important cause of neonatal morbidity and mortality worldwide. However, it is diagnostic challenge as there are overlapping signs and symptoms which preclude a specific diagnosis of sepsis. So, we have to rely on investigations to guide us. Blood culture has always been the gold standard for the diagnosis of neonatal sepsis. It has been noted that only 20% of symptomatic neonates with suspected early‑onset sepsis (EOS) have a positive blood culture, and only 30% neonates clinically suspected to have late‑onset sepsis (LOS) in neonatal intensive care unit (NICU) setting have a positive blood culture. [16,17] However, the blood culture report is available too late and it cannot be relied upon for making immediate decisions.

On comparing the platelet indices with the gold standard, the blood culture, thrombocytopenia (platelet count < 1.5 lakhs/ mm^3) was the most sensitive marker for sepsis, (83.08%). Previous studies have shown the sepsis screen to have variable sensitivity and specificity, because the timing of sample collection may affect its results. If sample is drawn several hours after illness or after starting antibiotics, sensitivity and specificity of sepsis screen will change. Moreover, CRP increases in other inflammatory conditions as well. [18] When we combine the existing sepsis screen and platelet indices and correlate it with blood culture, the specificity of diagnosis increases (46%). A high specificity was seen with a combination of sepsis screen with MPV + PDW + platelet count or sepsis screen with MPV + PDW which was 62.6% in both cases. However, there are no published data on correlation of sepsis screen with platelet indices for evaluation for neonatal sepsis. But the data from this study seem to indicate that a combination of sepsis screen with platelet indices can be used to reasonably rule out sepsis in each scenario.

To overcome these limitations, we usually rely on sepsis screening. But it has a variable sensitivity and specificity. The negative predictive value of these parameters is too low to confidently rule out sepsis. [19,20] The limitations of blood

culture, its low positivity rates, and poor diagnostic capability of sepsis screen in neonates make the diagnosis of sepsis difficult, and thus the need for better diagnostic parameters arises. [21]

Conclusion

NNT can be used as screening tool in NNS as it is easy and cost effective. It requires further large scale studies and meta-analysis to validate. Mortality in sepsis cases increases with severity of thrombocytopenia. Thrombocytopenia is a good prognostic marker of neonatal sepsis. Thus, it may be concluded that platelet indices are sensitive markers to identify septic babies and they may be combined with the existing sepsis screen to specifically exclude the diagnosis of neonatal sepsis.

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