Journal of Pregnancy and Child Health

Research Article Open Access

A Study of Neonatal Sepsis and its Relation to Thrombocytopenia in Neonates of Tertiary Care Hospital of Western Nepal

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Abstract

Introduction: Thrombocytopenia, defined as a platelet count below 150,000 cells/mm^3 is a frequent problem in neonatal intensive care units, complicating the clinical course in 22-35% of intensive care admissions. Recently, there has been wide interest in thrombocytopenia and especially the correlation between platelet count and clinically significant bleeding. One of the major cause of thrombocytopenia in neonates is sepsis.

Aims and objectives: The present study aimed to know the incidence of thrombocytopenia in neonatal sepsis and to evaluate the feasibility of neonatal thrombocytopenia as a screening tool for neonatal sepsis.

Materials and methods: This hospital based prospective observational cross sectional study was conducted in Neonatal Intensive Care Unit in Universal College of Medical Sciences, a tertiary care hospital, Nepal over a period of 3 months, from May 2019 to July 2019. A total of 205 Neonates was suspected sepsis under the age of 28 days admitted in NICU, were included in our study.

Results: A total of 205 Neonates with suspected sepsis, thrombocytopenia was found 81 (39.5%) babies, in which mild was 50 (24.4%), moderate was 25 (12.2%), severe 6 (2.9%) cases. 108(52.68%) mothers needed normal vaginal delivery and 97 (47.31%) mothers delivered by lower segment caesarean section.

Thrombocytopenia in weight for age was seen in 31 (15.12%) in small for gestational age (SGA) cases, 171 (83.41%) were showed in appropriate for gestational age (AGA) cases, 3 (1.46%) cases were showed in large for gestational age (LGA) babies. C-reactive protein was positive in 113 (55.12%) cases of thrombocytopenic babies whereas rest had negative CRP 92 (44.87%). blood culture was positive in 51 (24.9%) cases. the organism was isolated Coagulase Negative Staphylococcus species (CONS) is 22 (43.3%) and Kleibsella species 12 (23.52%) were the most common Gram positive and Gram negative organism.

Conclusion: It can be used as a screening tool for NNS as it is an easy and cost effective method.

Keywords: Neonatal sepsis (NNS); Neonatal thrombocytopenia (NNT); Neonates; Antibiotic

Introduction

Early-onset sepsis remains a common and serious problem for neonates, especially preterm infants. Group B streptococcus (GBS) is the most common etiologic agent, while *Escherichia coli* is the most common cause of mortality. Current efforts toward maternal intrapartum antimicrobial prophylaxis have significantly reduced the rates of GBS disease but have been associated with increased rates of Gram-negative infections, especially among very-low-birth-weight infants [1,2]. The diagnosis of neonatal sepsis is based on a combination of clinical presentation, the use of nonspecific markers, including C-reactive protein and procalcitonin (where available), blood cultures and the use of molecular methods, including PCR. Cytokines, including interleukin 6 (IL-6), interleukin 8 (IL-8), gamma interferon (IFN-) and tumor necrosis factor alpha (TNF-) and cell surface antigens, including Soluble Intercellular Adhesion Molecule (sICAM) and CD64, are also being increasingly examined for use as nonspecific screening measures for neonatal sepsis [3]. Viruses, in particular enteroviruses, parechoviruses and Herpes Simplex Virus (HSV), should be considered in the differential diagnosis [4]. Empirical treatment should be based on local patterns of antimicrobial resistance but typically consists of the use of ampicillin and gentamicin or ampicillin and cefotaxime if meningitis is suspected, until the etiologic agent has been identified.

It encompasses various systemic infections of the newborn such as septicemia, meningitis, pneumonia, pyogenic arthritis, osteomyelitis and urinary tract infections. Sepsis is the commonest cause of neonatal mortality; it is responsible for about 30-50% of the total neonatal deaths in developing countries. It is estimated that up to 20% of neonates develop sepsis and approximately 1% die of sepsis related causes. Sepsis related mortality is largely preventable with rational antimicrobial the rapid and aggressive supportive care [5].

Sola et al. showed that the likelihood of developing thrombocytopenia increases with the degree of prematurity [6]. Roberts et al., calculated that low-birth weight infants were at a 2.52-fold increased risk for thrombocytopenia [7]. Thrombocytopenia develops in 18-35% of neonates admitted to intensive care units. In addition, the rate and severity of thrombocytopenia in neonates of pregnancy-

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Received: August 06, 2019; **Accepted:** September 14, 2019; **Published:** September 21, 2019

Citation: Gupta BK, Gupta BK, Shrivastava AK, Chetri P (2019) A Study of Neonatal Sepsis and its Relation to Thrombocytopenia in Neonates of Tertiary Care Hospital of Western Nepal. J Preg Child Health 6: 421.

induced hypertensive mothers vary. Chakravorty et al. demonstrated that in most of cases of pregnancies complicated by preeclampsia that the usual course of thrombocytopenia includes diagnosis within the first 2-3 days and resolution by 7-10 days of life [8].

Platelet production or thrombopoiesis, is a complex process that results in the production of thrombopoietin as the thrombopoietic stimulus leading to the generation and proliferation of megakaryocyte progenitors.

Platelet Transfusions (PT) in Neonatal Thrombocytopenia (NT) are commonly administered to reduce the risk of bleeding. However, there are few evidence-based guidelines to inform clinicians' decision-making processes. Developmental differences in hemostasis and differences in underlying disease processes make it difficult to apply PT practices from other patient populations to neonates [9]. Specifically, it is important to identify neonates at risk of bleeding who would benefit from PT and to determine whether PT either abrogate or exacerbate common neonatal complications such as sepsis, chronic lung disease, Necrotizing Enterocolitis (NEC) and retinopathy of prematurity. Among 972 Very-Low-Birth Weight (VLBW) infants from a multicenter retrospective cohort study, Sparger et al. reported that 231 (24%) had received a total of 1002 PT. A large proportion of PT were given to VLBW infants with platelet counts greater than 50,000/μL. Additionally, they found that the severity of illness influenced transfusion decisions. However, the severity of NT did not correlate with the risk of Intraventricular Hemorrhage (IVH) and in contrast, PT did not reduce the risk of IVH [10].

In a large multi-center study, Wiedmmeier et al. defined neonatal thrombocytopenia as a platelet count less than 150,000 cells/mm^3 [11]. Neonatal thrombocytopenia has been categorized into two groups depending on the time of onset: early onset, which is within 72 h of life and the late onset, after 72 h of life [12,13]. The degree of severity of thrombocytopenia can be further subcategorized according to platelet count in affected individuals: Mild thrombocytopenia-platelet count 100000 to 150000 cells/mm^3, moderate thrombocytopenia-platelet count 50000 to 99000 cells/mm^3, severe thrombocytopenia-platelet count <50000 cells/mm^3 [11].

The classification of sepsis based on time of appearance as Early Onset Sepsis (EOS) or Late Onset Sepsis (LOS) is important as it helps in determining the most probable organism and mode of transmission and guide for empiric treatment. Thrombocytopenia is one of the early but non-specific indicators of neonatal sepsis. It can be caused by bacterial, viral, fungal and parasitic infections and other non-infectious causes. Bleeding is a major complication of thrombocytopenia but it is generally limited to infants with count <30000 cells/mm^3. Studies have shown that approximately 50% cases of culture proven sepsis have thrombocytopenia virtually any organism capable of causing sepsis can induce thrombocytopenia. Increased Platelet Volume (IPV) indicates an increased proportion of young platelets in the circulation [14].

Aims and objectives

The present study aimed to know the incidence of thrombocytopenia in neonatal sepsis and to evaluate the feasibility of neonatal thrombocytopenia as a screening tool for neonatal sepsis.

Materials and Methods

This hospital based prospective observational cross sectional study was conducted in Neonatal Intensive Care Unit in Universal College of Medical Sciences, a tertiary care hospital over a period of 3 months, from May 2019 to July 2019. Inclusion criteria were all newborn admitted to UCMS-TH NICU with screening positive sepsis or clinically suspected sepsis and neonates with presence of 2 or more risk factor positive were considered as suspected sepsis were included. Other neonates were excluded from study according to exclusion criteria. A total number of 205 neonates suspected sepsis under the age of 28 days admitted in NICU, were studied and included in our study.

Sepsis screening criteria

Absolute Neutrophil Count (ANC)<1800 cells/mm^3

Immature to total neutrophil (I/T) ratio >0.2

Total Leukocyte Count (TLC)<5000 cells/mm^3 or >20,000 cells/mm^3

CRP>6 mg/dL

Micro ESR (μ-ESR)>15 mm/1st h.

Platelets<150000 cells/mm^3.

Blood culture

All new borns with suspect sepsis and screen positive sepsis were subjected to blood culture, 2-3 ml blood was collected with strict aseptic precaution and collected in culture vials and sent to microbiology laboratory as per the hospital protocol.

Exclusion criteria

Mother with history suggestive of (s/o) ITP, SLE other autoimmune disorders, on medication during pregnancy (Sulfonamides, Quinine/Quinidine) (Thiazides, Tolbutamide, Vancomycin, Hydralazine and Heparin) Neonate with history s/o bleeding disorder in family, trisomies, Turner /Noonan's syndromes, TAR syndrome. Severe Rh-HDN (marked erythropoiesis is 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 had received IV antibiotics for ≥ 48 h prior to our study.

Ethical clearance

The approval of Institutional Review Committee of Universal College of Medical Sciences, Bhairahawa, Nepal was taken before the initiation of experiment. Registration No. UCMS/IRC/118/19. All the protocols and experiments were conducted in compliance with the ethical principles and guidelines

Statistical analysis

Data were processed manually and analyzed with the help of SPSS (Statistical package for social sciences) Version 16.0. Quantitative data were expressed as mean and standard deviation. Qualitative data were expressed as frequency and percentage and comparison carried by Chi-square ($\chi 2$) test. A probability (p) value of <0.05 was significant.

Results

A total of 205 neonates with suspected sepsis were included for the study and were evaluated accordingly.

During this study period, a total 205 newborn with clinically suspected sepsis were admitted. There were 128 (62.4%) Hindu, 53(25.9%) Muslim and others were 24 (11.7%). 148 (72.2%) male and 57 (27.8%) female neonate with male to female ratio of 2.59; However

108 (52.7%) were delivered by normal vaginal delivery and 97 (47.3%) were delivered by lower segment caesarean section. Maternal risk factor for sepsis were 61 (29.8%) and without risk factor for sepsis 144 (70.2%). PV leakage were present in 22 (10.7%) cases. 39 (19%) neonates were born low birth weight and 166 (81%) were normal weight (>2.5 kg). 38 (18.5%) were preterm, 159 (77.6%) were term baby and 8 (3.9%) cases were post-term baby (Table 1).

Table 2 out of 205 suspected neonatal sepsis cases 81 (39.5%) thrombocytopenia, in which mild is 50 (24.4%), moderate is 25 (12.2%), severe 6 (2.9%) (Table 2).

The total 205 cases were evaluated for sepsis, the blood culture was positive in 51 (24.9%) cases. In which Coagulase negative Staphylococcus species (CONS) 22 (43.3%) and Kleibsella species 12 (23.52%) were the most common Gram positive and Gram negative organisms (Table 3).

Blood culture and sensitivity platelets count category showed that: Out of 205 case, 51 (24.87%) case was present in culture positive cases in which: 1 (2.0%) was severe, 12 (23.5%) were moderate, 12 (23.5%) were mild and 26 (51.0%) had normal and remaining 154 (75.12%) cases were present in sterile cases out of which 5 (3.2%) were severe, 13 (8.4%) were moderate, 38 (24.7%) were mild and 98 (63.6%) were normal. The chi square value is 8.403 and its p-value is 0.038 and it is statically significant (Table 4).

Thrombocytopenia in mode of delivery showed that, out of 205 cases, 108 (52.68%) were seen in normal vaginal delivery among which 5 (4.6%) were severe, 6 (5.6%) were moderate, 27 (25.0%) were mild and 70 (64.8%) were normal and remaining 97(47.31%) cases seen were in lower segment cesarean section among which 1(1.0%) was severe, 19 (19.6%) were moderate, 23 (23.7%) were mild and 54 (55.7%) were normal type. The chi square test is 11.814 and p value is 0.008 and is statistically significant (Table 5).

Thrombocytopenia in weight for age showed that out of 205 cases, 31(15.12%) were showed in SGA case of which:- 1(3.2%) severe, 4 (12.9%) moderate and 12 (38.7%) mild type, remaining 171 (83.41%) were seen in AGA cases out of which: 5 (2.9%) severe, 21 (12.3%) moderate and 35 (20.5%) mild type and other 3 (1.46%) cases were showed in LGA and all of them were mild type. The chi square value is 13.567 and p value is 0.035 and it is statistically significant (Table 6).

Thrombocytopenia in C-Reactive Protein showed out of 205 cases 113 (55.12%) were seen in positive among which 6 (5.3%) were severe, 17 (15%) were moderate, 28 (24.8%) were mild type and 62 (54.9%) were normal type and remaining 92 (44.87%) were seen in CRP

S. N.	Category	Distribution	Frequency	Percentage
1	Religion	Hindu	128	62.40%
		Muslim	53	25.90%
		Others	24	11.70%
2	Sex	Male	148	72.20%
		Female	57	27.80%
3	Mode of delivery	NVD	108	52.70%
		LSCS	97	47.30%
4	Maternal risk factor for sepsis	Yes	61	29.80%
		No	144	70.20%
5	PV leakage>18 hrs.	Yes	22	10.70%
		No	183	89.30%
6	Maturity of baby	Pre-term	38	18.50%
		Term	159	77.60%
		Post-term	8	3.90%
7	Weight for age	SGA	31	15.10%
		AGA	171	83.40%
		LGA	3	1.50%
8	Low birth weight	Yes	39	19.00%
		No	166	81.00%

Table 1: Demographic data of neonatal sepsis (n=205).

S.N.	Severity	Platelets Count	Frequency	Percentage (%)
1	Severe	>0.5 Lakh	6	2.90%
2	Moderate	0.5-1 Lakh	25	12.20%
3	Mild	1-1.5 Lakh	50	24.50%
4	Normal	1.5-4.5 Lakh	124	60.50%
Total			**205**	**100**

Table 2: Severity of neonatal sepsis.

Organisms	Number	Percentage
Coagulase negative	22	43.13
Klebsiella species	12	23.52
Acinetobacter species	6	11.76
Pseudomonas aeruginosa	2	3.92
Enterococcus species	2	3.92
Methicillin resistant *Staphylococcus aureus.*	6	11.76
Citrobacter species	1	1.96
Total	**51**	**100**

Table 3: Distribution of isolated organism.

Blood culture and sensitivity	Platelet Count Category				Total
	Severe	Moderate	Mild	Normal	
Positive	1	12	12	26	51
	2.00%	23.50%	23.50%	51.00%	100%
Sterile	5	13	38	98	154
	3.20%	8.40%	24.70%	63.60%	100.00%
Total	6	25	50	124	205
	2.90%	12.20%	24.40%	60.50%	100.00%

Table 4: Blood culture and sensitivity* platelets count category cross tabulation.

Mode of delivery	Platelet Count				Total
	Severe	Moderate	Mild	Normal	
NVD	5	6	27	70	108
	4.60%	5.60%	25.00%	64.80%	100.00%
LSCS	1	19	23	54	97
	1.00%	19.60%	23.70%	55.70%	100.00%
Total	6	25	50	124	205
	2.90%	12.20%	24.40%	60.50%	100.00%

Table 5: Thrombocytopenia in mode of delivery.

Weight for Age	Platelet Count				Total
	Severe	Moderate	Mild	Normal	
SGA	1	4	12	14	31
	3.20%	12.90%	38.70%	45.20%	100.00%
AGA	5	21	35	110	171
	2.90%	12.30%	20.50%	64.30%	100.00%
LGA	0	0	3	0	3
	0.00%	0.00%	100.00%	0.00%	100.00%
Total	6	25	50	124	205
	2.90%	12.20%	24.40%	60.50%	100.00%

Table 6: Thrombocytopenia in weight for age.

CRP	Platelet Counts				Total
	Severe	Moderate	Mild	Normal	
Positive	6	17	28	62	113
	5.30%	15.00%	24.80%	54.90%	100.00%
Negative	0	8	22	62	92
	0.00%	8.70%	23.90%	67.40%	100.00%
Total	6	25	50	124	205
	2.90%	12.20%	24.40%	60.50%	100.00%

Table 7: Thrombocytopenia in C-reactive protein.

negative among which 8 (8.7%) were moderate, 22 (23.9%) were mild and 62 (67.4%) were normal type. The chi square value is 10.198 and its P value is 0.017 and it is statistically significant (Table 7).

Discussion

We conducted this study for 3 months periods at UCMS NICU Unit it was showed that occurrence of thrombocytopenia in the newborn treated at NICU was 39.5%, which proves that frequency of thrombocytopenia in our region is still high among the newborn hospitalized at the NICU. A similar study carried out in Indonesia showed that thrombocytopenia in the neonates hospitalized was 12% [15]. Gram positive bacteria coagulase negative was isolated as the most frequent cause of thrombocytopenia in the new born in our study (43.13%) and gram negative bacteria i.e. Kleibseilla was found to be second common cause of thrombocytopenia in the newborn (23.52%). Riedler et al. found that an 80% incidence of thrombocytopenia in gram negative septicemia and 65% of incidence in gram positive septicemia [14].

In this study we concluded in blood culture and sensitivity test of thrombocytopenia was found that 24.87% cases in blood culture positive and 75.13% in sterile cases. Similarly thrombocytopenia in normal vaginal delivery was found to be 52.68% and about 47.13% in lower segment cesarean section. Also thrombocytopenia was found maximum in appropriate for gestational age (AGA) i.e. 83.41% followed by SGA (15.12%) and then in LGA (1.46%). Thrombocytopenia was found more in CRP Positive cases 55.12% followed by CRP Negative cases which was 44.87%. Guida et al. had reported that 54% neonatal sepsis in Very Low Birth Weight (VLBW) neonates developed thrombocytopenia [16]. Khair et al. studied 'Role of Hematologic Scoring System in Early Diagnosis of Neonatal Septicemia they found that platelet count <1,00,000 cells/mm^3 had a sensitivity of 60%, specificity 82%, PPV 31% and NPV 94% [17]. A cross sectional analytical study on CRP and hematological parameters in NNS, in military hospital, Rawalpindi, over 7 months, it included 100 clinically septic and 100 normal neonates and observed that NNT has 64.3% sensitivity in detecting NNS. NNT is almost equal in normal (49.38%) and low birth weight (50.62%) neonates. NNT can be used as screening tool in NNS as it is easy and cost effective [18]. In the present study, blood culture positivity was observed in 51 (24.87%) neonates. thrombocytopenia was found in 81 (39.5%) suspected sepsis cases. 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. Therefore, it was observed from the study that platelet count is an important indicator of septicemia and not related with blood culture.

Conclusion

It was observed that the study of platelet count is an important indicator of septicemia and not related with blood culture and sensitivity. In the present study we found that NNT (<1,50,000 cells/mm^3) can be used to screen neonate with sepsis (NNS) especially in risk neonates which is cost effective and available in almost all hospitals. Early detection of thrombocytopenia in the newborn hospitalized in NICU, is emphasize because development of severe infection and at the same time high mortality in the risky group of the newborn can be prevented.

Acknowledgements

Authors would like to thank the department of Pediatric and Neonatal intensive Care and also thankful to Laboratory staff Unit of Universal College of Medical Sciences Bhairahawa, Nepal.

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