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Correlation between Late-onset Neutropenia, Sepsis and Associated Factors in Preterm Infants: A single center study

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ABSTRACT

Background: Late onset neutropenia (neutropenia after 3 weeks of life) may be a physiological condition without need to prescribe antibiotics, G-CSF, or IVIG. We aimed to determine the association between sepsis and late onset neutropenia in very low birth weight (<1500 gm) infants.

Methods: This study was a cross-sectional prospective study in VLBW infants that were admitted in Mahdieh Hospital in Tehran/Iran. Complete blood count (CBC) was drawn at first day of admission and then weekly intervals until discharge from the hospital. In cases with neutropenia, CRP and blood cultures were assessed and correlation between clinical sepsis or positive blood culture and CRP with neutropenia was evaluated.

Results: 219 VLBW infants during a period of 11 weeks were studied with serial weekly CBCs. 128 (58%) neonates had normal neutrophil counts, 91 (41.6%) had neutropenia, of which 28 (30.7%) had late onset neutropenia. Mean level of WBC was 5033.07±2037.57 cells/mm^3 and mean level of ANC was 1757.75±944.32 cells/mm^3. Positive blood culture at first week of life had significant correlation with neutropenia (P=0.001), but there was no significant correlation between late onset neutropenia and positive CRP (P=0.861), clinical symptoms of sepsis (P=0.5) and bacteremia (P=0.861). There was significant correlation between anemia (P<0.001) and IVH (P<0.007) without any significant correlation with asphyxia (P<0.223) and IUGR (P<0.123) with late onset neutropenia.

Conclusion: VLBW infants admitted to the NICU with late onset neutropenia without symptoms of sepsis do not need any intervention and close observation with follow-up would be the most appropriate approach.

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Introduction

Preterm births account for 11% of deliveries worldwide.[1] Almost 1.5-2% of the neonates are born as VLBW (birth weight less than 1500 grams.[2] Neutropenia defined as absolute neutrophil count (ANC) <1500 cells/mm^3 affects 6-58% of VLBW infants.[3] Early onset neutropenia (during the first two weeks of life) may be accompanied with maternal preeclampsia, sepsis, hypoxic-ischemic encephalopathy (HIE) and intraventricular hemorrhage (IVH).[4] Late-onset neutropenia means neutropenia at a postnatal age of more than 3 weeks that can be accompanied by neonatal late-onset sepsis or drug-induced neutropenia due to prolonged use of antibiotics or may be seen as a developmental physiological condition in bone marrow of preterm infants.[5]

Neutropenia and sepsis traditionally are suggested to have a cause and effect relationship with each other. Neutropenia and abnormal immature to total WBC ratio (I/T ratio) can be used as an early and sensitive laboratory test for diagnosis of sepsis.[6] Since neonatal

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sepsis can be fulminant and accompanied with high rate of morbidity and mortality, especially in preterm and VLBW infants, both over diagnosis and over treatment may be observed in many NICU units.[7, 8] In most cases of neonatal neutropenia, administration of antibiotics and G-CSF or IVIG for treatment of neutropenia and associated sepsis are administered.

Studies have shown that late onset neutropenia may be a benign type of bone marrow depletion without any association with fulminant sepsis,[9] thus the use of broad-spectrum and prolonged antibiotics in this conditions seems unreasonable and this approach may prolong hospital stay, increase microbial resistance due to more antibiotic usage and exposes the families to high cost of admission. There is some evidence for an association between hypoxic-ischemic encephalopathy (HIE), intraventricular hemorrhage (IVH) and intrauterine growth retardation (IUGR) with neonatal neutropenia.[10]

Hematologic disorders are one of the most common problems of preterm infants in NICUs.[11] Neutrophil development begins early in second trimester of pregnancy and continues until the term. Preterm delivery could be followed by defects in the maturation of fetal neutrophils and hence increases the risk of life-threatening infections in preterm neonates. There are some various developmental defects in preterm babies such as disorders in the ability of neutrophils to pass across the endothelial barrier and abnormalities in chemotaxis, respiratory burst, and degranulation.[12] Anemia, thrombocytopenia and neutropenia all can complicate the neonatal course of infancy, although physiologic changes of bone marrow activity without any association with pathologic conditions can cause physiologic events such as physiologic anemia and benign late-onset neutropenia.[13]

The aim of this research was to determine the incidence of neutropenia and concurrent anemia and thrombocytopenia in VLBW infants in NICU of Mahdieh Hospital. In addition, the association between late onset neutropenia and neonatal sepsis and other variables including HIE, IUGR, IVH and anemia of prematurity were the other objectives in the studied population.

Materials and Methods

This study was carried out as a cross-sectional observational prospective study in VLBW infants admitted in Mahdieh hospital in August-November 2015, a maternity center with 4000-5000 delivery annually with a 3% rate of VLBW delivery annually. The research was approved by the institutional review board of the Shahid Beheshti University of Medical Sciences and written consent was obtained from parents. All VLBW infants with birth weight <1500 gm and gestational age less than 32 weeks were enrolled into the study.

Complete blood count of the neonates was drawn at first day of admission and then in weekly intervals until 8 weeks or at the time of discharge from the hospital. In cases with clinical signs and symptoms suggestive of sepsis or neonates with neutropenia (regardless of clinical symptoms), CRP and blood cultures were also analyzed. In sick neonates with clinical symptoms of sepsis and in patients with positive blood culture and bacteremia, lumbar puncture was performed additionally. The correlation between clinical sepsis or positive blood culture and CRP with neutropenia was analyzed.

Neutropenia was defined as absolute neutrophil count <1500 cells/mm^3, late-onset neutropenia as neutropenia after first 3 weeks of life, leukopenia as leukocyte count <5000 cells/mm^3, thrombocytopenia as platelet count <150,000/ mm^3, anemia as hemoglobin <10 gm/dL or lower than 2 SD for gestational age and positive CRP when it was higher than 6 mg/dl. Variables such as gestational age, birth weight, sex, IUGR (birth weight lower than 10% for gestational age), IVH (recognized by brain ultrasound study), HIE (based on clinical symptoms of hypoxic-ischemic encephalopathy) and anemia of prematurity in late neutropenia were analyzed in our study.

Data were analyzed with SPSS (statistical package for the social science, Chicago, IL) software version 22. Quantitative and qualitative variables were described with mean±SD and frequency (percent), respectively. Repeated measure analysis variance and Pearson correlation test were used for data analysis. Test of normality was done with Shapiro-Wilks. P value<0.05 was considered statistically significant.

Results

During the study period, 219 VLBW infants were admitted in NICU. Among this population, 128 (58%) had normal leukocyte counts (5000-20000), 91 neonates (41.6%) had neutropenia and 28 (30.7%) had late-onset neutropenia. One hundred thirty-three (61%) were male and eighty-six (39%) were female. Mean level of WBC, hemoglobin, platelets, and ANC were: 10430.36/mm^3, 9.97 g/dl, 265000/mm^3, and 5038/mm^3, respectively. Mean level of WBC in group of neonates with late-onset neutropenia was 5033.07±2037.57/mm^3 and mean level of ANC was 1757.75±944.32/mm^3. Apgar score at 1 and 5 minutes were less than 7 in 50% and 32.1%, respectively in late-onset neutropenia. 8 neonates (30.8%) had symptoms suggestive of HIE, 8 (30.8%) were IUGR and 4 (14.3%) developped IVH. Anemia was observed in 24 neonates (88.8%) with late-onset neutropenia. There was an association between anemia (P<0.001) and IVH (P<0.007) with late-onset neutropenia; however, association between late-onset neutropenia with HIE (P<0.223) and IUGR (P<0.123) was not observed. There was not any significant association between positive CRP and clinical symptoms of sepsis with neutropenia except in the first week of life which positive blood culture had a significant correlation with neutropenia (P=0.001). In addition, there was not any significant correlation between positive CRP (P=0.861), clinical symptoms of sepsis (P=0.5) and bacteremia (P=0.861) (Table 1). There was a significant correlation between anemia of prematurity and neutropenia in our study which with increasing postnatal age, this correlation was more meaningful.

Discussion

One of the most common complications of prematurity is the occurrence of septicemia. Due to the prolonged

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Table 1: Correlation between neutropenia and signs and symptoms of sepsis

Age		CRP			Blood Culture			Clinical Symptoms	
+		-	P value	+	-	P value	+	P value	
At Birth	ANC<1500	3	1	0.054	4	2	0.423	6	0.6
	ANC>1500	14	0		14	3		17	
1st Week	ANC<1500	5	1	0.516	3	4	0.0001*	7	0.2
	ANC>1500	9	4		6	8		14	
2 nd Week	ANC<1500	1	0	0.439	0	1	0.676	1	0.05
	ANC>1500	8	5		3	17		20	
3 rd Week	ANC<1500	3	1	0.861	1	3	0.975	4	0.5
	ANC>1500	12	5		5	14		19	
4th Week	ANC<1500	2	0	0.121	1	3	0.807	4	0.1
	ANC>1500	4	6		5	11		16	
5th Week	ANC<1500	1	2	0.416	1	3	0.888	4	0.3
	ANC>1500	6	4		4	10		14	
6th Week	ANC<1500	1	1	0.427	0	4	0.31	4	0.5
	ANC>1500	4	1		3	8		11	
7th Week	ANC<1500	2	0	0.495	2	3	0.31	5	0.3
	ANC>1500	4	1		1	6		7	
8th Week	ANC<1500	2	1	0.709	2	2	0.277	4	0.5
	ANC>1500	1	1		2	5		7	

admission of a preterm infant in the hospital and the necessity of various manipulations, sepsis (consisting of early or late onset) can complicate the course of admission of the neonates in NICU.[14] Neutropenia in this population can be associated with maternal hypertension, sepsis, HIE and IUGR and is usually associated with clinical symptoms of respiratory distress syndrome or sepsis in neonates in first days of life, so that prescription of antibiotic and adjuvant therapies such as G-CSF and IVIG seems reasonable.[15, 16]

Considering that the neutropenia necessarily doesn't associate with sepsis, we this study to determine the association between late-onset neutropenia and signs and symptoms of septicemia in VLBW infants. The results of our study didn't show any significant correlation between late-onset neutropenia with clinical symptoms of sepsis, bacteremia and increased CRP. In a study by Omar and colleagues 22 % of 225 VLBW neonates had late-onset neutropenia without any association with signs and symptoms of sepsis and other problems such as nutritional and growth impairment.[4]

In agreement with the results of our study, Vetter-Laracy founded that 259 out of 401 neonates (65%) had late-onset neutropenia, while the rate of septicemia in neutropenic and non-neutropenic infants was similar (49% vs 47 %, P: 0. 674).[9] Another research in 2006 showed that 6–58% of preterm infants had low blood neutrophil counts at least once during their hospital stay.[17] In our study, 41.6% of neonates had neutropenia in course of their admission in NICU.

According to few studies, since most common causes of neutropenia in NICU units are due to other underlying disorders but sepsis, it could be concluded that little diagnostic evaluations even in cases with moderate to severe neutropenia is required.[18] In parallel to our study, Vetter-Laracy et al. reported that late-onset neutropenia was associated with IVH. This association was clinically significant in our study (P<0.007). In a study by Juul on 2038 neonates, 67% had normal range of neutrophil counts and 14% of them had neutropenia at some time during their hospital course. The prevalence of neutropenia was decreased with increasing postnatal age; 69% of neutropenia in the first week of life was observed in infants of mothers with pregnancy-induced hypertension.[19] The median age of neutropenia in VLBW infants in this research was 6 weeks, similar to our study that the nadir of ANC was seen in 7-8 weeks of life.

The strength of our research was the relatively prolonged (8 weeks) follow up of VLBW patients in NICU, whereas its limitation was low sample size of the patients especially neonates with late-onset neutropenia. Another limitation of our study was lack of follow up of preterm neonates after discharge from the hospital for determining the final course of neutrophil count.

Conclusion

We conclude that in VLBW infants with late-onset neutropenia without signs and symptoms of sepsis, close observation and follow up could be suggested as a preferred approach, although future researches with larger sample size and randomized control trials using antibiotics or other supportive measures such as G-CSF or IVIG are required.

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Conflict of Interest: None declared.

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