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Original Article

Neutrophil Counts in Hospitalised VLBW and ELBW Neonates – A Prospective Observational Study

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Abstract

Introduction: Early-onset sepsis (EOS) is an important cause of morbidity and mortality in new born babies and presents diagnostic challenges. The role of the neutrophil count in EOS in neonates has been studied extensively but with varying results.

Methods: A prospective observational study was conducted among very low birth weight (VLBW) and extremely low birth weight (ELBW) neonates. Complete blood count (CBC) was carried out for all neonates. Our primary objective was to study the neutrophil count in VLBW and ELBW neonates. Our secondary objectives were to study the total leucocyte count (TLC) along with the neutrophil count on day 1 in neonates with EOS and to study the neutrophil count in VLBW / ELBW neonates.

Results: Among the 175 neonates, 92 (52.6%) were males, and 83 (47.4%) were females. Mean birth weight was 1105 ± 241 g. Neutropenia was observed among 10 neonates on day 1, with a mean neutrophil count of 791.2 ± 315.8 / μL. Neutrophilia was observed among 27 neonates on day 1, with a mean neutrophil count of 9054.2 ± 3361.4 / μL. Compared with 18 out of 165 neonates without neutropenia, four out of 10 neonates with neutropenia on day 1 had EOS, which was statistically significant (P = 0.024).

Conclusions: Neutrophil count is a valuable indicator of sepsis among VLBW and ELBW neonates.

Introduction

Neutrophil counts and TLC are frequently used in the evaluation of sepsis in newborn babies. The TLC in healthy neonates varies widely from 5000 – 15000 /μL.[1] A TLC of < 5000 cells / μL (leukopenia) is believed to be a better predictor of septicaemia than leukocytosis.[2] Studies have reported that low TLC and a low absolute neutrophil count (ANC) are associated with increased odds of EOS.[2] Gerdes et al reported that the sensitivity and specificity of leukopenia were 26% and 91%, respectively in diagnosing septicaemia.[3]

Neonates with VLBW are at increased risk of EOS due to quantitative and qualitative neutrophil insufficiencies.[4] In VLBW neonates, the normal range of ANC is 1100 – 6000 / μL.[1] Newman et al reported that ANC on day 1 can be used to predict EOS.[5] Our primary objectives were to study neutrophil counts in

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VLBW / ELBW neonates and to study the TLC along with the neutrophil count on day 1 in neonates with EOS. Our secondary objective was to study neutrophil counts in VLBW / ELBW neonates born to mothers with PIH.

Methods

All VLBW and ELBW neonates admitted to the NICU at the Department of Paediatrics, Kasturba Medical College, Manipal, India from October 2014 to June 2016, who satisfied the inclusion criteria were recruited into the study. The study protocol was reviewed by the Institutional Ethics Committee and approved (IEC 648 / 2014). We included all inborn VLBW and ELBW neonates. We excluded all inborn neonates who had died within the first three days of life and neonates discharged against medical advice within the first three days. All neonates included in the study were evaluated by CBCs at admission. Data were collected as per the study protocol. Gestational age was determined by the last menstrual period (LMP), ultrasound or estimation by paediatricians. CBCs and differential counts were measured via an Abott Cell Dyn 3500 coulter at the Hematology Laboratory of Kasturba Hospital, Manipal, India. ANC was determined by multiplying the total white blood cell (WBC) count by the percentage of polymorphonuclear neutrophils, band forms, myelocytes and metamyelocytes. The corrected WBC count was calculated via the following formula:

Corrected WBC count = WBC count X 100 / nRBCs + 100 (nRBCs = nucleated red blood cells).[1] The range of normal TLC was 5000 – 15000 /μL.[1]

The study data were processed via SPSS Version 20.0. For the analysis of the baseline characteristics of the study group, descriptive statistics were used. For the variables following a normal distribution curve, the mean and standard deviation (SD) were computed. Fisher's exact test was used for the analysis of categorical variables between groups. Significance was assessed at the 5% level via a nonparametric 2-tailed test. A P value of < 0.05 was considered statistically significant.

Study definitions

- ◊ Neutropenia: condition characterised by a decreased ANC < 1100 / μL.[1]
- ◊ Neutrophilia: condition characterised by increased ANC > 6000 / μL.[1]
- ◊ Leukopenia: condition characterised by a decreased TLC < 5000 / μL.[1]
- ◊ Leukocytosis: condition characterised by increased TLC > 15000 / μL.[1]
- ◊ VLBW: neonates with birth weight ≤ 1500 g.[6]
- ◊ ELBW: neonates with birth weight < 1000 g.[6]
- ◊ Small for gestational age (SGA): defined as a birth weight below the 10th percentile for gestational age as per the Lubchenco chart.[6]
- ◊ Appropriate for gestational age (AGA): birth weight between the 10th and 90th percentiles for gestational age per the Lubchenco chart.[7]
- ◊ PIH: a sustained blood pressure (BP) of 140 / 90 mm Hg or greater during pregnancy associated with proteinuria.[8]
- ◊ EOS: a diagnosis of EOS was made if either clinical sepsis developed within 72 hours of life or if positive blood cultures were obtained in those with potential maternal risk factors.[9]

Results

The demographic characteristics of the neonates in our study are depicted in Table 1 and the TLC counts on day 1 and 3 is represented in Table 2. Similarly, neutrophil count on day 1 and day 3 in relation to gestational age is depicted in Table 3.

Table 1: Sample characteristics of the study population

Sample characteristics	Number of neonates (N = 175)	Percentage
Sex		
Male	92	52.6
Female	83	47.4
Birth weight (Grams)		
< 1000	58	33.1
1000 – 1500	117	66.9
Gestational age (Weeks)		
24 – 26	12	6.9
27 – 29	59	33.7
30 – 34	96	54.9
> 35	8	4.6
Gestation		
AGA	56	32
SGA	119	68
Birth weight (Grams)		
Mean ± SD	1105 ± 241	
Range	485 – 1499	
Gestational age (Weeks)		
Mean ± SD	30 ± 2	
Range	24 – 37	

On the first day of life, 78.8% had a normal WBC count, with a mean of 9436 ± 2439 / μL, ranging from 5100 – 14850 / μL. Leukocytosis was observed in 23 neonates (13.1%), with a higher mean WBC count of 19332 ± 6493 / μL, and leukopenia was noted in 14 neonates (8%), with a mean WBC count of 3854 ± 1046 / μL. By day 3, 81.1% of the neonates maintained a normal WBC count, with a slight increase in the mean WBC count to 9883 ± 2631 / μL. Leukopenia was more prevalent on day 3, occurring in

Table 2: Total leukocyte count on day 1 and day 3 among neonates (N = 175)

Day	Normal WBC Count	Leukocytosis	Leukopenia
Day 1 Number of neonates WBC count (/ μL) Mean ± SD Range	138 (78.8%) 9436 ± 2439 5100 – 14850	23 (13.1%) 19332 ± 6493 15100 – 46610	14 (93.3%) 3854 ± 1046 1300 – 4900
Day 3 Number of neonates WBC count (/ μL) Mean ± SD Range	142 (81.1%) 9883 ± 2631 5000 – 14900	14 (93.3%) 17342 ± 2261 15000 – 23700	19 (10.8%) 3866 ± 1137 890 – 4970

Table 3: Neutrophil count on day 1 and day 3 in relation to gestational age (N = 175)

Gestational age in weeks	Neutropenia		Normal neutrophil count		Neutrophilia	
	Day 1	Day 3	Day 1	Day 3	Day 1	Day 3
24 – 26 (N = 12)	0	1 (8.3%)	7 (58.4%)	11 (91.6%)	5 (41.6%)	0
27 – 29 (N = 59)	7 (11.9)	3 (5.1%)	43 (72.8%)	41 (69.5%)	9 (15.3%)	15 (25.4%)
30 – 34 (N = 96)	3 (3.1%)	1 (1.1%)	82 (85.4%)	74 (77%)	11 (11.4%)	21 (21.9%)
> 35 (N = 8)	0	0	6 (75%)	5 (62.5%)	2 (25%)	3 (37.5%)

19 neonates (10.8%), with a mean WBC count of 3866 ± 1137 / μL, whereas leukocytosis was observed in 14 neonates (8%), as depicted in Table 2.

As depicted in Table 3, majority of the neonates (54.85%) were in the gestational age group of 30 - 34 weeks. Among these patients, 85.4% and 77% had normal neutrophil counts on day 1 and day 3 respectively. One neonate in the 24 – 26 week gestational age group who experienced neutropenia at 72 hours died later due to sepsis.

On day 1, 78.8% of the neonates had normal neutrophil counts, with a mean ANC of 3149 ± 1357 / μL. Neutropenia was observed in 5.7% of the neonates, with a mean ANC of 791 ± 315 / μL. Neutrophilia was noted in 15.4% of the neonates, with a mean ANC of 9054 ± 3361 / μL. By day 3, there was a slight decrease in the proportion of neonates with normal neutrophil counts to 73.1%, although their mean ANC increased slightly to 3434 ± 1308 /μL. Neutropenia was observed in 2.8% of the neonates, with a mean ANC of 770 ± 406 / μL, whereas neutrophilia increased to 24%, with a mean ANC of 7743 ± 2418 / μL, as depicted in table 4. Comparison of total leucocyte count and neutrophil count on day 1 is shown in table 5. The association between leukopenia on day 1 and early-onset sepsis is represented in table 6 whereas association between neutropenia on day 1 and early-onset sepsis among neonates is shown in table 7. And the association between PIH and neutrophil count is depicted in table 8.

Among the 14 neonates with leukopenia, 42.8% had neutropenia. In contrast, among the 138 neonates with normal WBC counts, only 2.8% had neutropenia, and the majority (89.1%) had normal neutrophil counts. Neonates with leukocytosis tended toward neutrophilia, with 69.5% displaying elevated neutrophil counts.

Leukopenia on day 1 was significantly associated with EOS, as shown in Table 6. Among the 14 neonates with leukopenia, 35.7% developed EOS, whereas only 10.5% of neonates without leukopenia developed EOS, suggesting a strong correlation between low WBC counts and the risk of sepsis.

Neutropenia on day 1 was also found to be significantly associated with EOS. Among the 10 neonates with neutropenia, 40% developed EOS, whereas only 10.9% of the 165 neonates without neutropenia developed EOS which is illustrated in Table 7.

Among the 59 neonates born to mothers with PIH, 5% had neutropenia. However, this difference was not statistically significant compared with the 6% incidence of neutropenia in neonates born to mothers without PIH, as shown in table 8.

Table 4: Comparison of day 1 and day 3 neutrophil counts among neonates (N = 175)

Parameter	Neutropenia		Normal neutrophil count		Neutrophilia	
	Day 1	Day 3	Day 1	Day 3	Day 1	Day 3
Number of neonates	10 (5.7%)	5 (2.8%)	138 (78.8%)	128 (73.1%)	27 (15.4%)	42 (24%)
ANC*						
Mean	791 ± 315	770 ± 406	3149 ± 1357	3434 ± 1308	9054 ± 3361	7743 ± 2418
Range	130 - 1093	116 – 1069	1120 – 5948	1127 – 5940	6120 – 20042	2355 – 16116

*ANC in (/ μL)

Table 5: Comparison of total leucocyte count and neutrophil count on day 1 among neonates (N = 175)

Number of neonates	Neutropenia	Normal	Neutrophilia
Leukopenia (N = 14)	6 (42.8%)	8 (57.1%)	0 (0%)
Normal WBC count (N = 138)	4 (2.8%)	123 (89.1%)	11 (7.9%)
Leukocytosis (n=23)	0 (0%)	7 (30.4%)	16 (69.5%)

Table 6: Association between leukopenia on day 1 and early-onset sepsis among neonates (N = 175)

WBC count	EOS	No EOS	Odds ratio (95% CI)	P value
Leukopenia (N =14)	5 (35.7%)	9 (64.3%)	4.7059 (1.4128 – 15.6750)	0.0185
No leukopenia (N =161)	17 (10.5%)	144 (89.5%)	1	

Table 7: Association between neutropenia on day 1 and early-onset sepsis among neonates (N = 175)

WBC Count	EOS	No EOS	Odds ratio (95% CI)	P value
Neutropenia (N = 10)	4 (40%)	6 (60%)	5.4444 (1.4022 – 21.1395)	0.024
No neutropenia (N = 165)	18 (10.9%)	147 (89.1%)	1	

Table 8: Association between PIH and neutrophil count among neonates (N = 175)

	Neutropenia	No neutropenia	Odds ratio (95% CI)	P value
PIH (N = 59)	3 (5%)	56 (95%)	0.8342 (0.2077 – 3.3504)	1.0
No PIH (N = 116)	7 (6%)	109 (94%)	1	

Discussion

In our study, we observed variations in neutrophil counts based on gestational age, thus highlighting the influence of prematurity on the neonatal immune system. The data on neutrophil counts among term and late preterm neonates were first studied by Manroe et al, who reported that the neutrophil counts peaked at 12 – 24 hours with 95% confidence limits of 7800 – 14500 / μL and then reached a lower value of 1750 / μL by 72 hours of life.[10] In a study on ANC among healthy preterm VLBW neonates, Mouzinho et al described ranges that increased from approximately 500 / μL – 2200 / μL at 18 - 20 hours after birth and from 1100 / μL – 6000 / μL between 61 hours and 28 days, respectively.[1] In a study by Schmutz et al, the ANC between 72 and 240 hours after birth ranged from 2700 – 13000 / μL for infants > 36 weeks gestation, 1000 – 12500 / μL at 28 – 36 weeks gestation, and 1300 – 15300 / μL at < 28 weeks gestation.[11] The findings of our study are comparable with the studies in the past.[1,10,11] Low birth weight and gestational age are closely correlated with the incidence of neutropenia in neonates because of the nutritional deprivation and / or immune system maturation that occurs with age.[4]

In our study, we found a significant association between leukopenia and neutropenia on day 1 and EOS. In a study by Adane et al, leukopenia was observed in 26.6%

of neonates with sepsis.[12] Leukopenia has been shown to be a more accurate indicator of new born sepsis and can provide better information about infections resulting from gram-negative bacteria than leucocytosis.[4] In a large series of 166,092 neonates with suspected EOS studied by Hornik et al, low WBC counts, low ANC, and high immature-to-total neutrophil ratios were associated with increased odds of infection (Highest odds ratios: 5.38, 6.84, and 7.97, respectively).[13] Various other studies have also shown a direct association between neutropenia and sepsis, especially among preterm LBW neonates.[14-17] In a study by Shah et al among 542 neonates < 32 weeks gestation, leukopenia on day 1 was associated with higher odds of both EOS and late-onset sepsis (LOS) than with no leukopenia.[14] In a study by Teng et al, nosocomial infections affected 14% of ELBW neonates with neutropenia, compared with 20% without neutropenia, in the first 7 days following birth.[15] In contrast, many studies have established an association between high ANC and EOS.[18,19] A study by Panchal et al revealed that in new-borns with high ANC levels (> 5400 / μL), the occurrence of EOS was 9.35 times greater than that in peers with normal ANC (1800 – 5399 / μL).[18]

In our study, we did not find any association between neutropenia and PIH. In a study by Juul et al, neutropenia was observed in 42% of neonates, and it was inversely associated with maturity and directly associated with PIH.[20] Palta et al reported leukopenia in 27% of VLBW neonates < 32 weeks gestation, which was associated with higher rates of PIH.[21] Shah et al reported that rates of maternal PIH and SGA were higher in neonates with leukopenia than in those without leukopenia.[14] Doron et al reported that 48% of LBW infants from mothers with PIH experienced neutropenia at less than 12 hours of age.[22] The correlation between maternal PIH and neutropenia in newborns has been demonstrated by several other studies.[23-25]

The strengths of our study include longitudinal prospective sample collection through the first week of life in a large series of 175 preterm VLBW / ELBW neonates and detailed analysis of WBCs along with neutrophils from peripheral blood in real time. The limitations of the present study include the lack of analysis of other leukocyte populations, such as lymphocytes, immature forms, and their associations with EOS. We did not compare other outcomes of preterm birth as we focused on sepsis as the primary outcome.

Conclusions

Among VLBW / ELBW neonates, either leukopenia or neutropenia at birth was significantly associated with EOS. ANC can be used to predict EOS in neonates. Maternal PIH was not associated with neutropenia.

Conflict of Interest: None

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