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Original Research Article

Hematological parameters as predictors of short-term outcomes in perinatal birth asphyxia in term neonates: a prospective case-control study

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ABSTRACT

Background: Perinatal asphyxia is a significant cause of neonatal morbidity and mortality globally. Haematological changes, particularly in nucleated red blood cell (nRBC) counts, may offer early diagnostic and prognostic insights.
Objective: To estimate and compare haematological parameters in term neonates with and without birth asphyxia and to evaluate their association with short-term outcomes, including hypoxic ischemic encephalopathy (HIE) and meconium aspiration syndrome (MAS).
Methods: A hospital-based prospective observational case-control study was conducted among 170 term neonates, comprising 85 neonates with birth asphyxia and 85 healthy controls. Haematological parameters including haemoglobin, haematocrit, platelet count, total leukocyte count, absolute nRBC count and nRBCs/100 white blood cells (WBCs) were analysed within six hours of birth. Statistical analysis was performed using Student's t-test, Chi-square test and ANOVA, with $p<0.05$ considered statistically significant.
Results: Cases demonstrated significantly higher absolute nRBC counts (0.784±0.5957 vs. 0.0609±0.0156) and nRBCs/100 WBCs (2.3035±1.4014 vs. 0.6098±0.15633) compared with controls ($p<0.001$). Elevated nRBC levels showed significant associations with the severity of birth asphyxia, HIE staging, occurrence of MAS and prolonged hospital stay. Total leukocyte count was also significantly increased among cases, whereas haemoglobin, haematocrit and platelet counts did not differ significantly between the groups.
Conclusions: Absolute nRBC count and nRBCs/100 WBCs are inexpensive, readily available haematological markers that correlate with the severity and short-term outcome of perinatal asphyxia. Their incorporation into the routine evaluation of asphyxiated neonates may facilitate early risk stratification and prognostication.

Keywords: Hypoxic ischemic encephalopathy, Nucleated RBC, Perinatal asphyxia

INTRODUCTION

Perinatal asphyxia remains a significant contributor to neonatal mortality and long-term neurodevelopmental impairments globally. According to the World Health Organization, birth asphyxia affects approximately 3% of the 120 million infants born annually in developing countries, contributing to an estimated 900,000 neonatal deaths each year.[1] In India, birth asphyxia is one of the leading causes of neonatal mortality and contributes substantially to neonatal morbidity and mortality, as reported by the national neonatal perinatal database (NNPD).[2] Perinatal asphyxia is defined as the failure to initiate and sustain regular breathing at birth. The NNPD in India defines moderate birth asphyxia as an APGAR score of 4–6 and severe birth asphyxia as 0–3 at 1 minute.[2] The pathophysiology involves hypoxemia, hypercapnia, metabolic acidosis and multi-organ ischemic injury, with the brain being particularly vulnerable, often resulting in HIE, which remains a major

cause of neonatal morbidity and long-term neurological sequelae.[3]

While APGAR scores and imaging techniques remain standard for diagnosing asphyxia, haematological parameters such as nucleated red blood cells (nRBCs) have gained importance as potential early biomarkers.[4-6] Increased erythropoietin production during hypoxia induces premature release of erythroid precursors into circulation.[7,8] These changes can be used to estimate severity and predict short-term outcomes like HIE, MAS and mortality.[9-12]

Data evaluating the prognostic significance of haematological parameters among Indian term neonates remain limited. Therefore, the present prospective case-control study was undertaken to evaluate and compare haematological parameters between asphyxiated neonates and healthy term neonates and to examine the relationship between these parameters and clinical outcomes.

METHODS

This prospective, hospital-based case-control study was carried out to estimate and compare the haematological parameters in asphyxiated term neonates and healthy term neonates as well as to determine which haematological parameter amongst asphyxiated neonates can predict short term outcome like HIE and MAS. The study was conducted over a period of 18 months from February 2021 to July 2022 in the NICU and post-natal ward of a department of Pediatrics at a tertiary care teaching hospital after taking ethical approval from Institutional Review board of the Hospital.

Sample size and study population

The sample size was calculated using Epi Info™ software based on the mean absolute nucleated red blood cell (nRBC) counts reported by Ferns et al.[10] A 99% confidence level, 80% study power and a 1:1 case-to-control ratio were considered for sample size estimation. Based on these assumptions, the minimum required sample size was 170 term neonates, comprising 85 cases and 85 controls.

A total of 170 term neonates were enrolled in the study and divided into two groups.

Cases (n=85)

Term neonates with moderate to severe perinatal asphyxia (APGAR score <7 at 1 minute).

Controls (n=85)

Healthy term neonates with normal perinatal transition without clinical evidence of birth asphyxia.

Inclusion criteria

Term intramural neonates (gestational age ≥37 weeks) with clinical evidence of moderate or severe perinatal asphyxia and an APGAR score of less than 7 at one minute of life were included in the study.

Exclusion criteria

Neonates with major congenital malformations, small-for-gestational-age status, maternal diabetes mellitus, Rh isoimmunization, maternal magnesium sulphate therapy or other significant maternal medical disorders were excluded. Neonates who died within the first 24 hours of life or whose parents declined consent were also excluded.

Data collection

After taking Informed consent from the Parents of Neonates admitted in the NICU and Pots-natal ward of the hospital, data collection was done using pre-structured proforma to enter patient's detailed clinical history, Demographic data, obstetric and labour history, need for resuscitation, APGAR at 1 and 5 min and outcome. According to NNPD 2000, the cases were grouped into moderate (APGAR 4-6 at 1 min) and severe (APGAR <3 at 1 min) birth asphyxia and as per Sarnat and Sarnat scoring system cases were classified into HIE stage I, II, III groups depending upon neurological examination findings.[2,4]

Haematological evaluation

Blood samples drawn within first six hours of birth, from both cases and controls, were used for making smears by VCS (Volume conducting scatter) method and also processed by Beckman coulter machine for obtaining complete blood count in 5 parts.

Following parameters were obtained from the blood samples: haemoglobin concentration (g/dl), haematocrit (%), total leukocyte count (cells/mm^3), Platelet count (×10^3/µl), absolute nRBC count and nRBCs per 100 white blood cells (Leishman-stained peripheral smear).

Outcome measures

The primary objective was to compare haematological parameters between asphyxiated and healthy term neonates. Secondary objectives included evaluating the association of nRBC count and nRBCs per 100 WBCs with the severity of birth asphyxia, hypoxic ischemic encephalopathy, meconium aspiration syndrome, duration of hospital stay and neonatal outcome.

Statistical analysis

Data were analysed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables were

expressed as mean±standard deviation, while categorical variables were expressed as frequencies and percentages. Student's t-test, Chi-square test and one-way analysis of variance (ANOVA) were used for statistical comparisons where appropriate. A p value of less than 0.05 was considered statistically significant.

RESULTS

Demographic and clinical characteristics

A total of 170 neonates were enrolled in this prospective observational case control study, with 85 neonates with perinatal birth asphyxia (cases) and 85 healthy term neonates (controls) during the study period of 18 months (Figure 1).

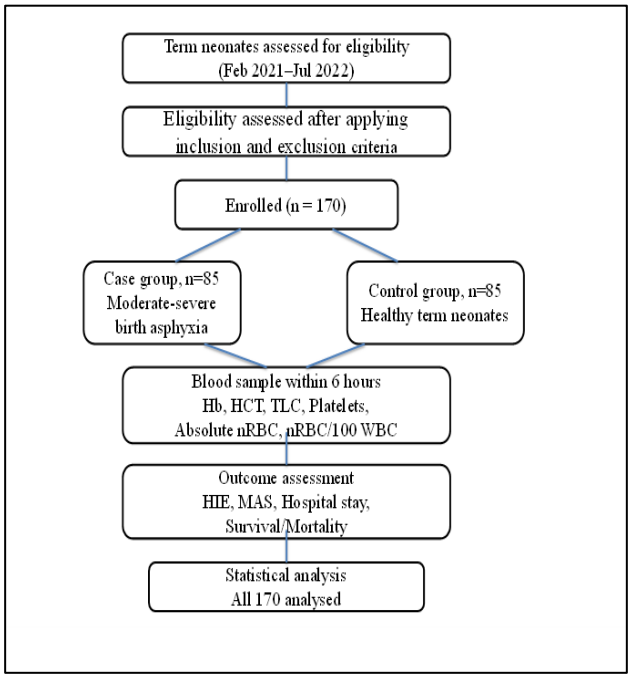

Figure 1: Study flow-chart.

The demographic and clinical characteristics are summarized in Table 1. The mean birth weight was comparable between the two groups (2.79±0.34 kg among cases vs. 2.81±0.34 kg among controls), with no statistically significant difference (p=0.59). Similarly, Gender was also comparable across the cases and control groups (p=0.87).

However, the mean gestational age was significantly lower in the asphyxiated group (38.42±1.27 weeks) compared to controls (38.87±1.26 weeks, p=0.02). The maternal age was also significantly lower in the case group (23.71±3.60 years) compared to controls (26.71±4.10 years, p<0.001). A significantly greater proportion of neonates in the case group were delivered by lower segment caesarean section (LSCS), whereas all control neonates were delivered either vaginally or by assisted vaginal delivery (p<0.001). Primigravida mothers constituted a significantly higher proportion of cases compared with controls (p=0.025) (Table 1).

Comparison of haematological parameters

The comparison of haematological parameters between the two groups is shown in Table 2. The mean haemoglobin and haematocrit levels were slightly higher in asphyxiated neonates than controls, but did not reach statistical significance (p=0.09 and p=0.43, respectively). Platelet counts also did not differ significantly between the two groups (p=0.09). In contrast, total leukocyte count was significantly elevated among neonates with birth asphyxia (20,266±6,081 cells/mm³) compared with controls (9,478±2,933 cells/mm³; p<0.001).

The most significant findings were observed in nucleated red blood cell parameters. Mean absolute nRBC count was markedly higher in cases than controls (0.784±0.5957 versus 0.0609±0.0156; p<0.001). Likewise, mean nRBCs per 100 white blood cells were significantly increased among asphyxiated neonates (2.3035±1.4014 versus 0.6098±0.1563; p<0.001), indicating a strong association between elevated nRBC levels and perinatal hypoxic insult (Table 2).

Association of nRBC count with severity of birth asphyxia and clinical outcome

Table 3 illustrates the relationship between haematological parameters (nRBCs and nRBCs/100 WBCs) and severity and clinical outcomes of birth asphyxia. When categorized by severity of asphyxia, neonates with severe asphyxia (APGAR 0–3) exhibited significantly higher nRBCs and nRBCs/100 WBCs values versus those with moderate asphyxia (APGAR 4–6), with highly significant p values (<0.001). Similarly, neonates who developed MAS demonstrated significantly higher nRBC counts and nRBCs per 100 WBCs compared with those without MAS (p<0.001). A progressive rise in nRBCs and nRBCs/100 WBCs was observed with increasing severity of HIE. Mean nRBC values increased from 0.14±0.21 in HIE stage 0 to 0.84±0.11 in HIE stage III. Similarly, nRBCs/100 WBCs rose from 0.99±1.24 to 3.0±1.82 across the same range indicating a positive correlation between erythroid response and severity of hypoxic injury (p<0.001).

Neonates with hospital stay <7 days had a mean nRBC count (0.30+0.35), while those staying >7days had a significantly higher mean nRBC count (084+0.86), similarly, the maen nRBC/100 WBC was markedly elevated in neonates with longer hospitalization (2.25+1.22) compared to those with shorter stay (1.23+1.24, p<0.001). Furthermore, neonates who expired had higher nRBC values (0.82±0.16) and nRBCs/100 WBCs (2.50±1.47) than those who were discharged (0.36±0.56 and 1.30±1.21, respectively), with all associations reaching statistical significance (p<0.001), reinforcing the prognostic value of these

haematological markers. Overall, elevated nRBC count and nRBCs per 100 WBCs demonstrated significant associations with the severity of birth asphyxia, HIE staging, MAS, prolonged hospital stays and neonatal mortality, supporting their utility as early prognostic biomarkers in perinatal asphyxia.

Table 1: Demographic and clinical variables.

Variables		Case (n-85) N (%)/ Mean±SD	Control (n-85) N (%)/ / Mean±SD	P value
		Neonatal variables		
Birth weight (kg)		2.786±0.3444	2.814±0.3409	0.59
Male gender		47(55.3%)	48(56.7%)	0.87
Gestational age (in weeks)		38.423±1.2759	38.870±1.2610	0.02
		Maternal variables		
Age (in years)		23.705±3.6082	26.717±4.0959	<0.001
Gravida	Primi	33 (38.8%)	26 (30.56%)	0.025
	Multi	52 (61.2%)	59 (69.4%)	
Mode of delivery	LSCS	22 (25.9%)	-	<0.001
	NVD	52 (61.2%)	85 (100%)	
	VAD	11 (12.9%)	-	

Table 2: Comparison of haematological parameters between cases and controls.

Variables	Case (n-85) / Mean±SD	Control (n-85) / Mean±SD	P value
Haemoglobin(gm/dl)	15.812±2.5368	15.242±1.8234	0.09
Haematocrit(%)	50.6600±9.1529	49.762±5.3675	0.43
Platelet ($\times10^3$ /ul)	213.4±82.3	182.27±152.26	0.09
nRBCs ($\times10^3$ /ul)	0.784±0.5957	0.0609±0.0156	<0.001
nRBCs/100 WBCs	2.3035±1.4014	0.6098±0.15633	<0.001
Total leucocyte count	20266±6081.73	9477.6±2933.23	<0.001

Table 3: Association of nRBC and nRBC/100 WBCs with severity and outcome of birth asphyxia among cases.

Outcome		nRBC (mean±SD)	nRBC/100WBCs (mean±SD)	P value
Severity of Birth asphyxia	Moderate (APGAR 4-6)	2.446±0.615	2.284±1.191	<0.001
	Severe (APGAR 0-3)	2.666±0.608	2.431±1.209	
MAS present		0 .78±0.19	2.57±0.468	<0.001
No HIE		0.14±0 .21	0.99±1.24	<0.001
HIE stage I		0.71±0 .17	2.0±0.86	<0.001
HIE stage II		0.80±0.79	2.17±0.69	<0.001
HIE stage III		0.84±0 .11	3.0±1.82	<0.001
Hospital stays	0-7 days	0.30±0.35	1.23±1.24	<0.001
	>7 days	0.84±0.86	2.25±1.22	
Discharged		0.36±0.56	1.30±1.21	<0.001
Died		0.82±0.16	2.50±1.47	<0.001

DISCUSSION

The present prospective case-control study evaluated the role of haematological parameters, particularly nRBC count and nRBCs per 100 WBCs, as predictors of disease severity and short-term outcome in term neonates with perinatal birth asphyxia. The findings demonstrate that these haematological markers are significantly elevated in asphyxiated neonates and show a strong association with the severity of hypoxic insult and adverse neonatal outcomes. In the present study, total leukocyte count, absolute nRBC count and nRBCs per 100 WBCs were significantly higher among neonates with birth asphyxia than healthy controls. These findings are consistent with previous studies by Phelan et al, Ghosh et al and Mohanty et al who reported that fetal hypoxia stimulates erythropoietin production, resulting in accelerated erythropoiesis and premature release of nucleated erythrocytes into the peripheral circulation.[6,7,12] The rise in total leukocyte count may represent the physiological stress response associated with perinatal hypoxia. Although haemoglobin concentration and haematocrit values were marginally higher in the asphyxiated group, the differences were not statistically significant. Similar observations have been reported by Brucknerová et al suggesting that haemoglobin concentration alone has

limited value in predicting the severity of perinatal hypoxia.[13] Platelet counts also showed no significant difference between the two groups, indicating that platelet count is a relatively poor independent marker of birth asphyxia. The present study further demonstrated that neonates with MAS had significantly higher nRBC counts and nRBCs per 100 WBCs than neonates without MAS. Meconium aspiration is frequently associated with chronic intrauterine fetal distress and prolonged hypoxia, explaining the increased erythropoietic response observed in these neonates. The findings corroborate those of Rai et al and Ghosh et al who linked raised nRBCs to adverse perinatal outcomes, including MAS and early neonatal complications.[7,15] The analysis of APGAR scores and asphyxia severity further strengthened the findings. A significant relationship was observed between nRBC count and the severity of birth asphyxia. Neonates with severe asphyxia (with 1-minute APGAR score 0–3) demonstrated higher nRBC counts than those with moderate asphyxia (with 1-minute APGAR score 4–6).

These findings support the hypothesis that increasing fetal hypoxia stimulates greater erythropoietin-mediated erythropoiesis, leading to increased peripheral release of immature erythroid cells. These differences were not evident with 5-minute scores, suggesting early hypoxic impact triggers hematopoietic response even before resuscitative improvement is seen. Similar observations have been documented by Shah et al, Ferns et al and Mohanty et al.[9,10,12] An important finding of the present study was the progressive increase in nRBC count and nRBCs per 100 WBCs with advancing stages of HIE. Neonates with HIE stage III demonstrated the highest values, indicating a direct relationship between haematological response and severity of neurological injury. Comparable findings have been reported by Ferns et al, Korst et al and Jena et al supporting the role of nRBC count as a useful early prognostic biomarker in neonatal hypoxic-ischemic injury.[10,11,16]

Aligning with their findings, in present study, nRBC and nRBC/100 WBC values showed a graded increase with advancing HIE stage, MAS and mortality.

The present study also demonstrated that elevated nRBC counts were associated with prolonged hospital stay and neonatal mortality. Neonates requiring hospitalisation beyond seven days and those who died during admission exhibited significantly higher nRBC values than survivors with shorter hospital stays. These observations reinforce the prognostic significance of nRBC count and suggest that this inexpensive and readily available investigation may assist clinicians in early risk stratification and intensive monitoring of neonates with birth asphyxia. Similar conclusions have been reported by Phelan et al, Mohanty et al and Jena et al.[6,12,16]

The principal strength of this study lies in its prospective design and inclusion of an age-matched healthy control group, allowing direct comparison of haematological parameters between asphyxiated and non-asphyxiated neonates. However, the study was conducted at a single tertiary care centre with a relatively modest sample size, which may limit the generalis ability of the findings. Larger multicentre studies are required to establish standard diagnostic cut-off values for nRBC count and to evaluate its role in predicting long-term neurodevelopmental outcomes.

Overall, the findings of the present study support the use of absolute nRBC count and nRBCs per 100 WBCs as simple, inexpensive and readily available biomarkers of perinatal hypoxia. Their significant association with birth asphyxia severity, HIE staging, MAS, prolonged hospital stay and mortality highlights their potential role in the early prognostic evaluation and management of affected neonates.

Strengths

The present study employed a prospective case-control design with a well-defined control group, enabling direct comparison of haematological parameters between asphyxiated and healthy term neonates. The study also evaluated the association of nRBC count with multiple clinically relevant outcomes, including HIE staging, MAS, duration of hospital stays and mortality, thereby enhancing its clinical applicability.

Limitations

The study was conducted at a single tertiary care centre with a relatively limited sample size, which may restrict the generalizability of the findings. Long-term neurodevelopmental follow-up was not performed; therefore, the relationship between nRBC count and long-term neurological outcomes could not be assessed. In addition, serial measurements of nRBC count were not undertaken and only early neonatal haematological parameters were evaluated.

CONCLUSION

The present study clearly establishes relationship between haematological parameters and perinatal asphyxia and its outcome. Among the various haematological parameters evaluated, nRBC and nRBC/100WBCs count emerged as the most useful early biomarker of hypoxic insult, reflecting both the severity of fetal hypoxia and short-term clinical outcome. As estimation of nRBC count is simple, inexpensive, minimally invasive and readily available in most healthcare settings, it may serve as a valuable adjunct to routine clinical assessment in neonates with suspected perinatal asphyxia.

Early identification of high-risk neonates using nRBC count may facilitate prompt intensive monitoring and timely therapeutic interventions, thereby improving neonatal outcomes. Incorporation of nRBC estimation into routine evaluation protocols for perinatal asphyxia

may therefore have significant clinical utility, particularly in resource-limited settings.

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