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Umbilical cord blood nucleated red cell count as a marker of perinatal asphyxia

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ABSTRACT

Background: Nucleated RBCs are a common observation in the circulating blood of newborn. Number of nRBC in cord blood and perinatal asphyxia shows good correlation. Perinatal asphyxia ranks as the second most important cause of neonatal death after infections accounting for about 30% mortality worldwide. Objective of the present study was designed to find the relation between umbilical cord blood nRBC count and perinatal asphyxia.

Methods: The present one-year prospective case control study was carried out. A total of 100 babies divided into two groups of 50 each as cases and controls. Term babies with perinatal asphyxia were enrolled as cases and term babies without perinatal asphyxia born during same period were included as control.

Results: The distribution of cord blood pH in cases showed maximum babies (80%) with pH value of <7 and 38% of the children were detected to have HIE stage II followed by 26% with stage I and 4% with stage III. At admission, 48 hours and 72 hours, significantly higher number of babies were found to have higher cord blood nRBC count (p<0.001) and the mean cord blood nRBC count was found to be significantly high at all the intervals (p <0.001). Comparison of mean cord blood nRBC count among cases in stage III was significantly high compared to stage II and I (p<0.001) at admission, 48 hours and 72 hours.

Conclusions: Cord blood nRBC can be used as surrogate marker for asphyxia. The clearance of nRBC from the circulation may be of help in prognosticating the outcome of asphyxiated babies.

Keywords: Cord blood nucleated red blood cell, Hypoxic ischaemic encephalopathy, Perinatal asphyxia

INTRODUCTION

Perinatal asphyxia is any perinatal resulting in suffocation with anoxia and increased carbon dioxide. Severe fetal hypoxia or ischaemia can manifest in the new born as encephalopathy and may result in neonatal death or permanent motor and mental disability. It is a serious problem globally and is one of the common causes of neonatal mortality. Perinatal asphyxia ranks as the second most important cause of neonatal death after infections accounting for about 30% mortality

worldwide.¹ Over 9 million children die each year during the perinatal and neonatal periods, and nearly all of these deaths occur in developing countries.³ Perinatal asphyxia is a serious clinical problem globally.

Every year approximately 4 million babies are born asphyxiated; this results in 1 million deaths and an equal number of serious neurological consequences ranging from cerebral palsy and mental retardation to epilespsy. This condition occurs in 2-10% of deliveries. Perinatal asphyxia is a major factor contributing to perinatal and

neonatal mortality, which is an indicator of the social, educational and economic standards of a community. Of the 1.2 million neonatal deaths in India every year, 300, 000 to 350,000 infants die due to perinatal asphyxia mostly within first three days of life.⁵

Taking into account that neonatal deaths account for almost 40% of death of children under 5, it is apparent that Millennium Development Goal 4 (aiming at a two-third reduction in under five mortalities by the year 2015 from a baseline in 1990) can only be met by substantially reducing neonatal deaths. Perinatal asphyxia is the fifth largest cause of under-five deaths (8.5%) after pneumonia, diarrhoea, neonatal infections and complications of preterm birth.¹

Perinatal asphyxia refers to a condition of impaired gas exchange that leads, if persistent, to fetal hypoxemia and hypercarbia.⁶ It occurs during the first and second stage of labour. The American Academy of Pediatrics has proposed the term perinatal asphyxia should be reserved to describe an infant who manifests with umbilical cord artery pH of less than 7.0; neonatal neurological suggestive manifestation of hypoxic ischemic encephalopathy (HIE); persistence of Apgar score of 0 to 3 at or after 5 minutes of birth. Evidence of multisystem dysfunction (e.g. cardiovascular, gastrointestinal, hematologic or pulmonary).⁷

World Health Organization (WHO) has defined perinatal asphyxia as a failure to initiate and sustain breathing at birth.² The National Neonatal Perinatal Database (NNPD), 2000 used a similar definition for perinatal asphyxia. It defined moderate asphyxia as slow gasping breathing or an Apgar score of four to six at one minute of age. Severe asphyxia was defined as no breathing or Apgar score of zero to three at one minute of age.⁵

Means of assessment include umbilical pH, 1-hour postdelivery blood gas, Apgar scores, and neurological changes ranging from twitching to hypotonia and seizures. Several other methods liker markers (nonprotein bound iron, interleukin-6), EEG, cerebral function monitoring, imaging modalities (USG, CT, MRI) have been developed for early identification of neonates at high risk for brain injuries who may benefit from early neuroprotective interventions like induced hypothermia, antioxidant agents (allopurinol) and calcium channel blockers.8-12 Further complications can be anticipated and corrective and preventive measures can be undertaken.

Most of the diagnostic and prognostic parameters used are available in few selected tertiary care hospital, are expensive and require sophisticated equipment's thus rendering them unreachable for most of the population. When resources are lacking in the developing countries, perinatal asphyxia can be crudely assessed by use of the Apgar score. Apgar scores at 10 minutes provide useful prognostic data before other evaluations are available for

infants. Low Apgar scores at 1, 5 and 10 minutes have been found to be markers of an increased risk of death or chronic motor disability. More scientific methods have been used, but this is not possible in settings where resources are scarce. Holia problem is further compounded in country like India where there is a wide gap between the need and accessibility of health services. Therefore, there is a need for simple tests to identify perinatal asphyxia.

Studies have been done to correlate number of nucleated red blood cells (nRBC) in cord blood with perinatal asphyxia and they have shown good correlation. 14-17 Increase in nRBC has been proposed due to increase production of erythropoietin secondary to perinatal asphyxia. 18 It is a simple test which can be done in a basic setup, available even in the primary health centers, which are the backbone of health care delivery in rural areas. Hence the present study was planned to assess relation between umbilical cord blood nucleated red cell and perinatal asphyxia. Objectives of this study was to assess relation between umbilical cord blood nRBC count and perinatal asphyxia.

METHODS

The study design was prospective case control study. The present study was conducted at department of Pediatrics during the period of one year. Neonates fulfilling the selection criteria were selected and their next of kin or legal guardians were briefed about the purpose of the study and a written informed consent was obtained. Institutional ethical committee clearance was obtained prior beginning of the study.

Source of data

Term babies with perinatal asphyxia formed the study sample and term babies without perinatal asphyxia born during same period were enrolled as controls.

Sample size

The present study was done on a total of 100 children divided into two groups of 50 each that is case and controls.

Sample size calculation

Less than three percent of normal newborn babies have elevated nRBCs. Therefore P_0 =0.03. Odds ratio to demonstrate a significant correlation equal to 10. Therefore, with $\alpha = 0.05$ and one-sided power of 80%.

 $P-(P_0+P_1)/2$

 P_1 - Number of asphyxiated babies with elevated nRBC count. 2α - Alpha error (1.65). 2β - Beta error (0.84).

Based on this formula the minimum effect size was calculated as 35 in each group. However, 50 children fulfilled the selected criteria and were included.

Inclusion criteria

- Term neonates with perinatal asphyxia, satisfying two or more of the following criteria;
- Apgar <6 at 5 mins.
- Umbilical cord arterial pH <7.00.
- Decelerations in fetal heart rate (Late decelerations with decreased beat-to-beat variability or variable decelerations.)
- Term newborns delivered during the same period with Apgar score ≥8 at 5 minutes were enrolled as controls.

Exclusion criteria

- Newborn with congenital malformations.
- Sepsis
- Rh incompatibility.
- Maternal diabetes mellitus.
- Mothers with ITP
- Mothers on drugs which change hematological profile like thiazides, angiotensin converting enzyme inhibitors, beta blockers.

Data collection procedure

Details of the maternal parameters like age, haemoglobin level, gestational data, medications taken, medical history, past obstetric history, present pregnancy, labour and delivery were recorded in a proforma. Details of the baby like weight, sex, Apgar score, gestational age, resuscitation was recorded. The Apgar scores of the newborns were assessed at one and five minutes. All newborns will be resuscitated as per AAP guidelines. HIE was graded using Sarnot staging. ¹⁹

Procedure

- A 0.5ml of cord blood was collected in a heparinized one cc syringe from maternal side before cutting the cord for obtaining the umbilical cord blood pH, which was carried out by "Rost Omni C" blood gas system.
- At birth two ml of cord blood was collected in both ethylene diamine tetra acetate and plain bulbs from both cases and controls. Samples were stored at room temperature if there is any delay in processing. Blood samples were used for making smears (for nRBCs), complete blood count and septic profile (to rule out sepsis). Babies, who have positive septic profile, as defined by presence of band forms or toxic granules or C reactive protein or thrombocytopenia, where excluded from the study.
- One ml of venous blood was collected from both cases and controls in ethylene diamine tetra acetate

- bulbs and 49 hours from making smeara (for nRBCs).
- Samples were processed and analyzed by the same blinded pathologist. The ethylene diamine tetra acetate samples were processed by "Coulter LH 500" counter for obtaining total white cell count and platelet count. The smears ere stained by Leishman's stain and manual differential count was done to count nRBCs, toxic granules and band forms.²⁰

Statistical analysis

Data obtained was coded and entered into Microsoft Excel spreadsheet. The categorical data was expressed as rates, ratios and percentages. Continuous data was expressed as mean±standard deviation (SD). The comparison between two groups for categorical data was carried out using chi-square test and continuous data was analyzed based on independent sample 't' test. A probability value of less than 0.050 was considered as statistically significant.

RESULTS

Table 1: Comparison of mean age, duration of labour, gestational age, birth weight between cases and control group.

Variables	Cases (n=50)		Controls (n=50)		р
	Mean	SD	Mean	SD	value
Maternal age (year)	23.00	2.43	23.96	2.56	0.057
Mean duration (hour)	10.65	2.08	9.85	2.23	0.067
Gestational age (week)	39.24	1.13	39.48	1.19	0.307
Birth weight (gm)	2622.00	352.00	2610.00	382.00	0.867

In the present study the mean maternal age was 23.00 ± 2.43 years in cases while in controls it was found to be 23.96 ± 2.56 years. However, the difference was statistically not significant found (p = 0.057).

In this study, the mean duration of labour was slightly high in cases and controls $(10.65\pm2.08 \text{ hours vs} 9.85\pm2.23 \text{ hours})$ but the difference was statistically not significant (p=0.067).

Table 2: Presentation at delivery.

Presentation	Cases (n=50))	Controls (n=50)		
Presentation	Frequency	%	Frequency	%	
Breech	3	6.00	1	2.00	
Cephalic	46	92.00	49	98.00	
Transverse lie	1	2.00	0	0.00	
Total	50	100.00	50	100.00	

 $p=0.351 \ (Chi \ square \ test)$

In this study, the mean gestational age in cases and controls was comparable (39.24±1.13 weeks vs 39.48±1.19 weeks) and found to be not significant (p=0.307). In this present study, the comparison of mean birth weight in cases (2622±352gm) and controls (2610±382gm) showed no statistically significant difference (p=0.867). In the present study, among cases and controls cephalic presentation was noted as most common presentation 92% an 98% respectively but on comparison between cases and control, the difference was statistically not significant (p=0.351).

Table 3: Comparison of mean Appar score in cases and control group.

Interval at	Cases Controls		n rolus		
(minutes)	Mean	SD	Mean	SD	p value
1	4.14	1.04	6.96	0.57	<0.001*
5	6.26	0.96	8.80	0.40	<0.001*

Table shows mean Apgar score at one minute and five minutes. It was observed that, at both the intervals, mean apgar score was significantly high in control compared to cases (p<0.001).

Table 4: Distribution of cases according to cord blood pH.

Cond blood nII	Cases (n=50)			
Cord blood pH	Frequency	Percentage		
<7	40	80.00		
7 to 7.2	10	20.00		
>7	0	0.00		
Total	50	100.00		

In this study the distribution of cord blood pH in cases showed maximum babies (80%) with pH value of <7 followed by 20% with pH value between 7 to 7.2.

Table 5: Distribution of cases according HIE staging.

IIIE stadina	Cases (n=50)	
HIE staging	Frequency	Percentage
None	16	32.00
Stage I	13	26.00
Stage II	19	38.00
Stage III	2	4.00
Total	50	100.00

In the present study 38% of the children were detected to have HIE stage II followed by 26% with stage I and 4% with stage III.

Table 6: Comparison of mean cord blood nRBC in cases and control group.

Interval	Cases (n=50)		Controls (n=50)		p value
	Mean	SD	Mean	SD	
At admission	35.98	22.36	11.92	7.74	<0.001*
48 hours	28.74	21.31	6.54	4.84	<0.001*
72 hours	22.32	19.06	3.80	4.46	<0.001*

^{*}Independent sample 't' test

The above table shows mean cord blood nRBC count in cases and controls at admission, 48 hours and 72 hours after admission. At admission, mean cord blood nRBC was significantly more in cases (35.98 ± 22.36) than control (11.92 ± 7.74) (p<0.001).

Table 7: Comparison of mean nRBC in different HIE stages at admission.

Interval	IIIE storing	Cases (n=50)		Engles	
	HIE staging	Mean	SD	F value	p value
	None	24.00	13.62		<0.001*
At	Stage I	23.38	9.63	22,479	
admission	Stage II	48.32	18.33	22.479	
	Stage III	96.50	0.71		
	None	20.19	10.16	17.367	<0.001*
48 hours	Stage I	18.54	9.06		
46 110018	Stage II	36.16	20.95		
	Stage III	93.00	2.83		
72 hours	None	14.88	10.46	20.257	۰۵ ۵۵1 *
	Stage I	13.54	7.73		
	Stage II	28.11	17.06	20.257	<0.001*
	Stage III	84.00	8.49		

^{*}One-way ANOVA

At 48 hours, mean cord blood nRBC was significantly more in cases (28.74 ± 21.31) than control (6.54 ± 4.84)

(p<0.001). At 72 hours, mean cord blood nRBC was significantly more in cases (22.32±19.06) than control

(3.80±4.46) (p<0.001). In the present study, comparison of mean cord blood nRBC count among cases at admission, 48 hours and 72 hours between HIE stages. It was observed that at admission, mean nRBC count was high at stage III (96.50±0.71) as compared to stage I (23.38±9.63) and II (48.32±18.33), and shows statistical significant difference between stages (p<0.001). At 48 hrs, mean nRBC count was high at stage III (93.0±2.83) as compared to stage I (18.54±9.06) and II (36.16±20.95), and shows statistical significant difference between stages (p<0.001). At 72 hrs mean nRBC count was high at stage III (84.0±8.49) as compared to stage I (13.54±7.73) and II (28.11±17.06) and shows statistical significant difference between stages (p<0.001).

DISCUSSION

Perinatal asphyxia is an insult to the fetus or new born due to lack of oxygen (hypoxia) and/or lack of perfusion to various organs. Diagnosis of hypoxic ischemic encephalopathy (HIE) requires an abnormal neurological examination on the 1st day of birth and evidence of an asphyxiating event taking place in the perinatal period. In asphyxiated neonates there are many biochemical and haematological variations like acidosis, abnormal electroencephalogram, altered blood flow, hypoxia and hypercarbia etc; Many studies in recent past have suggested that an increase number of nucleated red blood cells(NRBC) in umbilical cord blood may be a useful marker to identify birth asphyxia.²¹

Nucleated RBCs are a common observation in the circulation blood of new born. They are primarily produced in the fetal bone marrow in response to erythropoietin and are stored in the marrow as precursors to reticulocytes and mature erythrocytes. Many acute and chronic stimuli cause increase in the number of circulating NRBCs from either increased erythropoietic activity or a sudden release from the marrow storage pools. The number of NRBC/100 WBC is quite variable but is rarely more than 10. It is a simple test which can be done in a basic setup, available even in the primary health centers (PHC, which are the backbone of health care delivery in rural areas. The present study was designed to find the relation between umbilical cord blood nRBC count and perinatal asphyxia.

In the present study most of the mothers presented with age from 22 to 25 years (74% in cases and 66% in controls). The mean maternal age was 23.00 ± 2.43 year in cases while in controls it was found to be 23.96 ± 2.56 years. In cases, 58% and 40% of the babies in controls were males with male to female ratio of 1.38:1 in cases and 1:1.5 in controls. These findings suggest that the demographic characteristics were comparable in cases and controls (p>0.05).

In the present study with regard to birth history, cephalic presentation was noted commonly in cases and controls that is, 92% and 98% respectively. The mode of delivery

in 46% of the babies in cases was normal vaginal route compared to 70% of the babies in control group and LSCS was noted in 38% and 28% of the babies in cases and control groups respectively suggesting high incidence of LSCS in perinatal asphyxia group. Observation made by Fern et al also showed high incidence of emergency LSCS (39.28%) in perinatal asphyxia group, whereas spontaneous vaginal delivery in all controls.¹⁴

In this study, majority of mothers in cases (76%) and controls (90%) had less than 12 hours duration of labour. The mean duration of labour was comparable in cases and controls (10.65 ± 2.08 hours vs 9.85 ± 2.23 hours). In cases, 58% and 66% of the babes in controls had gestational age of more than 40 weeks. The mean gestational age in cases and controls was comparable (39.24 \pm 1.13 weeks 39.48 \pm 1.19 weeks). Most of the babies weighted between 2500 to 3499gm in cases (48%) as well as controls (44%). The comparison of mean birth weight in cases and controls showed no statistically significant difference (2622 \pm 352gm vs 2610 \pm 382gm; p=0.867). These findings indicate that the maternal and birth history in cases and controls was comparable.

In the present study, the cord blood pH in cases showed maximum babies (80%) with pH value of <7. Of the 50 babes, 38% of the children were detected to have HIE stage II followed by 26% and 4% with stage I and II.

In the present study, at admission, maximum babies had cord blood nRBC count between 21 to 40 (36%), 41 to 60 (22%), 61 to 80 (10%) and 81 to 100 (4%) compared to controls that is maximum babies had cord blood nRBC count of 20 or less (88%) (p<0.001). Similar findings were recorded at 48 hours of the admission were cord blood nRBC count between 21 to 40 was noted in 48% of the cases compared to 2% in controls (p<0.001). Even at 72 hours duration cord blood nRBC count was found to be up to 20 in 68% of the babies from cases compared to all the babies in controls (100%) (p<0.001). The mean cord blood nRBC count in cases and controls at admission (35.98±22.36 vs 11.92±7.74), 48 hours (28.74±21.31 vs 6.54±4.84) and 72 hours after admission (22.32±19.06 vs 3.80±4.46) was found to be significantly high (p<0.001).

Merenstein et al observed high nRBC counts in new born infants after acute or chronic antenatal asphyxia.²⁴

Recently Goel M et al from India reported significantly lower nRBC count in non-asphyxiated neonates i.e., 5.9 ± 2.6 compared to the asphyxiated group i.e., 29.5 ± 26.0 , and it had a p< $0.001.^{21}$

Ferns et al reported similar significant difference in the nRBC count between cases Vs controls and between various stages of HIE (p<0.000).¹⁴ Fotopoulos et al reported that increase in the number of nRBC is an early marker for subsequent neurological impairment.²³

Similar observations were made in their study of 14 and 78 asphyxiated and non-asphyxiated neonates respectively, found that asphyxiated group had a high NRBC count than the control group. 25-27

Buonocore et al in his study concluded that increase in NRBC count at birth not only reflects a response of the infant to perinatal hypoxia but is also a reliable index of perinatal brain damage.¹⁷

In this study comparison of mean cord blood nRBC count among cases in stage III was significantly high compared to stage II and I (p<0.001) at admission, 48 hours and 72 hours. Goel M et al evaluated the relationship between HIE staging and nucleate RBC and found that higher the HIE staging, higher was the mean nRBC. It was observed that in HIE stage 1 mean NRBC/100 WBC was $10.17\pm2.64.^{21}$ It was 19.04 ± 6.86 and 45.14 ± 32.41 for stages II and III respectively.

Overall the present study showed that, the cord blood nRBCs has a potential of being used as a simple marker for determining the severity and predicting the in-hospital pre-discharge outcome of fetal asphyxia. The limitations of the study were that, the study involved only term new born therefore it cannot be generalized to whole neonatal population. Further studies including term and preterm babies with special focus on its value as a part of scoring system would further enlighten the role cord blood nRBC in perinatal asphyxia.

CONCLUSION

Based on findings of the present study it may be concluded that, nucleated red blood cell can be used as surrogate maker for asphyxia. It is a simple bed side test that can be utilized to diagnose perinatal asphyxia in health centers where facilities for determining cord blood pH are not available. The clearance of nRBCs from the circulation may be of help in prognosticating the outcome of asphyxiated babies.

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Ethical approval: The study was approved by the

Institutional Ethics Committee

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