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RESEARCH ARTICLE

TO CORRELATE MATERNAL AND CORD BLOOD NUCLEATED RED BLOOD CELL COUNTS WITH PERINATAL OUTCOME IN NORMOTENSIVE AND PRE-ECLAMPTIC WOMEN

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ABSTRACT

Introduction: Increase in the number of circulating Nucleated Red Blood Cell (NRBC) may result from various stimuli. NRBC count in umbilical venous blood of neonates has been reported as a possible marker of perinatal asphyxia.

Aims The aim of the study was to correlate NRBC /100 WBC count with perinatal outcome in normal and pre-eclamptic women.

Materials and Methods: It was a prospective case controlled study performed on 120 normotensive and 120 pre-eclamptic women. At delivery 1 ml of umbilical cord blood and 1ml of maternal blood was collected and analyzed for NRBC. Mean cord blood NRBC /100 WBC count was correlated with perinatal outcome in normal and pre-eclamptic women.

Results: The mean maternal and cord blood NRBC counts in pre-eclamptic women was significantly higher than normotensive women (p<0.001). As the nucleated RBC count increased in maternal blood and cord blood, there was statistically highly significant decrease in mean neonatal birth weight and mean APGAR score and statistically highly significant increase in NICU admission and perinatal mortality in all women and pre-eclamptic women.

Conclusion: Neonates with elevated cord blood NRBC counts are more likely to have low birth weight, low APGAR score, neonatal ICU admission and perinatal mortality. Cord blood NRBC count is a simple test which is cost-effective. It provides valuable information about the well being of the newborn. The determination of NRBC count in cord blood can be used as an additional tool in the diagnosis of fetal asphyxia and predicting early perinatal outcome.

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INTRODUCTION

Nucleated red blood cells (NRBC) 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 and considered as haematologic markers for placental dysfunction, hypoxemia and asphyxia. Various parameters used to predict perinatal outcome or asphyxia are: intrapartum fetal monitoring, meconium-stained amniotic fluid, fetal or umbilical cord pH measurement, APGAR score, hypoxic ischemic encephalopathy (HIE), and major organ disorder. Effective prediction of perinatal asphyxia cannot be made by single marker and combination of indices are required for early diagnosis of perinatal asphyxia. (Ghosh *et al*., 2003; Volpe, 2001) Recently, the count of umbilical cord NRBC for every 100 white blood cells has been introduced as a marker of perinatal asphyxia. The number of circulating NRBC/100 WBC is quite variable, but normally it is rarely more than 10. (Phelan *et al*., 1995; Green and Mimouni, 1990; McCarthy *et al*., 2006) Increase in the number of circulating NRBCs may result from various stimuli which increase either erythropoietic activity or cause a sudden release from the marrow storage pools (Ruth *et al*., 1988) such as prematurity, intrauterine growth restriction, maternal hypertension, pre-eclampsia, Rh isoimmunisation, maternal smoking, maternal diabetes. NRBC counts in umbilical venous blood of neonates has also been reported as a possible marker of perinatal asphyxia. (Ghosh *et al*., 2003; Green and Mimouni, 1990; Hermansen *et al*., 2001) Increase in NRBC count is also seen in neonates with meconium aspiration syndrome. (Dollberg *et al*., 2001;

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Darkhaneh *et al*., 2008) Pre-eclampsia is considered to be a state of deterioration of utero–placental perfusion and disturbed feto-maternal cell trafficking which leads to raised maternal NRBCs and chronic hypoxia. (Holzgreve *et al*., 1998) The hypoxic event induces erythropoesis as a compensatory response, resulting in the release of nucleated red blood cells into the fetal circulation therefore adverse perinatal outcome may be reflected by NRBC count elevation at birth or persistence. The present study was undertaken to correlate NRBC /100 WBC count with perinatal outcome in normal and pre-eclamptic women.

MATERIALS AND METHODS

It was a hospital based observational study, done in the Department of Obstetrics & Gynaecology, S.M.S. Medical College, Jaipur. 120 normotensive and 120 preeclamptic women with singleton term pregnancy who were willing to participate in the study were included after obtaining informed written consent on first come first basis. Women with IUFD, congenital malformation and with pre existing hypertensive, cardiovascular or renal disease, diabetes mellitus or chronic disease were excluded from the study. The minimum criteria for preeclampsia was blood pressure ≥140/90 after the 20th week of gestation and proteinuria of over 300 mg/dl in 24 hours or dipstick results of ≥1+ in random samples. A detailed history and examination was done and investigations were done. Immediately after delivery of the fetus the umbilical cord was double-clamped and 1 ml umbilical cord blood was collected in a tube containing 1.5 mg ethylene diamine tetra-acetic acid (EDTA). 1 ml of maternal venous blood was collected in the same manner simultaneously. Blood films were prepared and stained using the leishman stain for 20 min. The number of NRBCs per 100 leukocytes was counted. Neonatal birth weight, APGAR at 5 min, IUGR, NICU admission and Perinatal mortality were noted. All data were entered on MS excel sheet and analyzed. Quantitative data were summarized in form of mean and S.D. (Standard Deviation) and the difference in means were analyzed in using student 't' test or anova test. Association of NRBC with neonatal weight and APGAR was done by Pearson cofficient correlation.

Observations

Both normotensive and pre-eclamptic groups were comparable in terms of maternal age, parity, period of gestation. The mean maternal NRBCs / 100 WBCs was 5.85 ± 4.022 in pre-eclamptic women as compared to 2.33 ± 2.571 in normotensive women and the difference was statistically significant (P < 0.001). The mean cord blood NRBCs in pre-eclamptic women was 16.19 ± 7.052 and mean NRBCs in normotensive women was 5.41 ± 3.91 the difference was statistically significant (P < 0.001). (Table 1) Mean maternal NRBC count was1.65 ± 1.31in 65.84% women, 6.90 ± 0.80 in 18.33%, 10.03 ±1.40 in 12.5% and 13.25 ±0.46 in 3.33% women. As the nucleated RBC count per 100 WBC increased in maternal blood, there was statistically highly significant decrease in mean neonatal birth weight (from 2.8 ±0.30 to 2.1 ±0.35) and mean APGAR score (from 8.15 ± 0.97 to 7.13 ±1.25) and statistically highly significant increase in NICU admission (from 7.6% to 62.5%) and perinatal mortality (from4.4% to 26.7%). (Table 2) Mean cord blood NRBC count observed was 2.14 ± 1.62, 7.80 ± 1.41, 12.49 ± 1.41, 18.00 ± 1.44, 22.18 ± 1.28 and 27.33 ± 1.22 in 29.17%, 23.33%, 19.58%, 11.25%, 11.67% and 5.00% women respectively. As the nucleated RBC count per 100 WBC increased in cord blood, there was statistically highly significant decrease in mean neonatal birth weight (from 2.9 ± .20 to 2.1 ± 0.49) and mean APGAR score (from 8.46 ± 0.74 to 6.85 ± 1.05) and statistically highly significant increase in NICU admission (from 2.9% to 58.3%) and perinatal mortality (from 2.9% to 25.0%). (Table 3) Table 4 shows association of mean cord blood NRBC with neonatal outcome in normotensive and pre-eclamptic women. When mean cord blood nucleated RBC count was compared in normotensive and pre-eclamptic women the difference was statistically highly significant for all the parameters of neonatal outcome.

Out of 240 pregnant women 61.7% delivered normally and 38.3% delivered by LSCS and the difference in mean cord blood nucleated RBC count in both the groups was statistically highly significant (p value 0.0001). The difference in mean cord blood nucleated RBC count in normotensive women was statistically not significant (p value 0.2) whether delivered vaginally or by LSCS while in pre-eclamptic women this difference was again significant (p value 0.002). Out of 240 babies, 77.9% babies had birth weight ≥ 2.5 Kg and mean cord blood nucleated RBC count was 9.22 ± 7.38 and 22.1% babies had birth weight < 2.5 Kg and mean cord blood nucleated RBC count was 16.21± 7.16 the difference in mean cord blood nucleated RBC count was statistically highly significant (p value 0.0001). The difference in mean cord blood nucleated RBC count for babies having birth weight <2.5 Kg and ≥ 2.5 Kg was statistically highly significant for normotensive as well as pre-eclamptic women. Out of 240 babies, 81.3% babies had APGAR ≥ 7 and mean cord blood nucleated RBC count was 9.25 ± 7.37 while 18.7% babies had APGAR < 7 and mean cord blood nucleated RBC count was 17.33 ± 6.55. The difference in nucleated RBC count was statistically highly significant (p value 0.0001). The mean cord blood nucleated RBC count was more in babies who had APGAR score < 7 than those who had APGAR score ≥ 7 in both normotensive and pre-eclamptic women but the difference was statistically not significant (p value 0.1) in normotensive women while in pre-eclamptic women the difference was statistically significant (p value 0.02). The mean cord blood nucleated RBC count was more in babies who required NICU Admission than for those who did not require NICU Admission. The difference was statistically not significant (p value 0.4) in normotensive women but the difference was statistically highly significant for all (p value 0.0001) and pre-eclamptic women (p value 0.0001). It was also observed that there is a statistically significant difference in mean NRBC count between the surviving neonates and in the neonates who expired with a higher count in the latter ((p value 0.0001). Table 5 shows the coefficient correlation linear regression analysis between the NRBCs of babies with birth weight and APGAR score at 5 min. A significant negative correlation was found with cord blood NRBC count and neonatal birth weight (R= - 0.5225) (fig 1) stating that as Birth weight decreased the NRBC increased and vice-versa.

Table 1. Mean maternal and Mean cord blood NRBCs count in normotensive and Pre eclamptic women

Variable	Total (n = 240)	Normotensive women (n = 120)	Pre-eclamptic women (n = 120)	P value
Mean maternal NRBC count	4.09 ± 3.80	2.33 ± 2.57	5.85 ± 4.02	<0.001, Sig
Mean cord blood NRBC count	10.8 ± 7.85	5.41 ± 3.91	16.19 ± 7.05	<0.001, Sig

Table 2. Association of Maternal NRBC count with Neonatal Outcome

Maternal NRBC Count	Total Number of women	Mean Maternal NRBC Count	Mean Weight	Mean APGAR Score	NICU Admission required	Perinatal mortality occurred
1 – 4	158 (65.84)	1.65 ± 1.31	2.8 ±0.30	8.15±0.97	12/158 (7.6%)	7/158 (4.4%)
5 – 8	44 (18.33)	6.90 ± 0.80	2.4 ±0.48	7.41 ±1.20	18/44 (40.9%)	6/44 (13.6%)
9 – 12	30 (12.50)	10.03 ±1.40	2.3 ±0.57	7.27 ±1.23	10/30 (33.3%)	8/30 (26.7%)
13 – 16	8 (3.33)	13.25 ±0.46	2.1 ±0.35	7.13 ±1.25	5/8 (62.5%)	2/8 (25.0%)
P value			0.0000 highly sig	0.0000 highly sig	0.0000 highly sig	0.0000 highly sig

Table 3. Association of Cord blood NRBC count with Neonatal Outcome

Cord blood NRBC Count	Total Number of women (n=240)	Mean Cord NRBC Count	Mean Weight	Mean APGAR Score	NICU Admission required	Perinatal mortality occurred
1 - 5	70 (29.17)	2.14 ± 1.62	2.9 ± .20	8.15 ± 0.80	2/70 (2.9%)	2/70(2.9%)
6 - 10	56(23.33)	7.80 ± 1.41	2.8 ±0.38	8.46 ± 0.74	4/56 (7.1%)	5/56(8.9%)
11 - 15	47(19.58)	12.49 ±1.41	2.7 ±0.43	7.98 ± 1.21	5/47(10.6%)	1/47(2.1%)
16 - 20	27(11.25)	18.00 ±1.44	2.4 ±0.42	6.85 ± 1.05	12/27(44.4%)	5/27(18.5%)
21 - 25	28(11.67)	22.18 ±1.28	2.2 ±0.46	6.89 ± 1.07	15/28(53.6%)	7/28(25.0%)
26 - 30	12(5.00)	27.33 ±1.22	2.1 ±0.49	7.33 ± 1.32	7/12(58.3%)	3/12(25.0%)
P value			0.0000 highly sig	0.0000 highly sig	0.0000 highly sig	0.0000 highly sig

Table 4. Association of Neonatal outcome with mean cord NRBC count in normotensive and pre-eclamptic women

Variable	Total no of women (n=240)	Mean Cord NRBC Count	Normotensive women (n=120)		Pre-eclamptic women (n=120)		P value
			No	Mean Cord NRBC Count	No.	Mean Cord NRBC Count	
				Mode of Delivery.			
Normal Delivery	148 (61.7%)	9.25 ± 7.29	82 (68.3%)	5.07 ± 3.92	66 (55.0%)	14.44 ± 7.20	0.0001
LSCS	92 (38.3%)	14.25 ± 6.51	38 (31.7%)	5.89 ± 3.88	54 (45.0%)	18.33 ± 6.29	0.0001
	0.0001 highly sig			0.2 ns		0.002 sig	
				Neonatal Weight			
≥ 2.5 Kg	187(77.9%)	9.22 ± 7.38	106(88.3%)	4.90 ± 3.75	81(67.5%)	14.88 ± 7.14	0.0001
< 2.5 Kg	53(22.1%)	16.21± 7.16	14(11.7%)	8.64 ± 3.61	39(32.5%)	18.92 ± 6.09	0.0001
	0.0001 s			0.0006 s		0.002 s	
				APGAR Score			
≥ 7	195(81.3%)	9.25 ± 7.37	116(96.7%)	5.23 ± 3.89	79(65.8%)	15.14 ± 7.32	0.0001
< 7	45(18.7%)	17.33 ± 6.55	4(3.3%)	8.25 ± 3.77	41(34.2%)	18.22 ± 6.09	0.002
	0.0001 s			0.1 n s		0.02 s	
				NICU Admission			
Yes	45(18.8%)	18.56 ± 6.81	6(5.0%)	6.5 ± 3.39	39(32.5%)	20.41± 5.07	0.0001
No	195(81.2%)	8.96 ± 6.96	114(95.0%)	5.37 ± 3.94	81(67.5%)	14.16 ± 7.00	0.0001
	0.0001 s			0.4 n s		0.0001 s	
				Perinatal Mortality			
Yes	23(9.6%)	16.52 ± 8.39	5(4.2%)	4.6 ± 3.36	18(15.0%)	19.83± 5.92	0.0001
No	117(90.4%)	10.15 ± 7.58	115(95.8%)	5.37 ± 3.94	102(85.0%)	15.55 ± 7.06	0.0001
	0.0004 s			0.7 n s		0.01 s	

Table 5. Correlation of nucleated RBC count with neonatal weight and APGAR score

N = 240	Mean ± SD	R	R square	Equation	P-value
Cord blood NRBC count	10.76 ± 7.87				
Neonatal weight	2.7 ± 0.44	- 0.5225	0.2730	Y = -0.0295*X + 2.99	0.0001 highly significant
APGAR score	7.87 ± 1.12	-0.4017	0.1614	Y = -2.805*X + 32.87	0.0001 highly significant

The R^2 is 0.2730 it means only 27% of the total variation in neonatal birth weight was explained by the linear relation with cord blood NRBC count. Similarly significant negative correlation was also found with APGAR score at 5 minute and cord blood NRBC count. (R= - 0.4017) stating that as APGAR score decreased the NRBC increased and vice-versa. The R^2 is 0.1614 it means only 16% of the total variation in APGAR score was explained by the linear relation with cord blood NRBC count. (Fig.2)

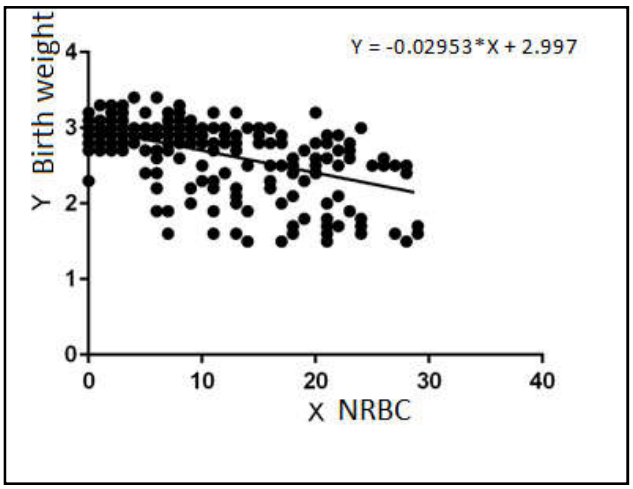

Fig. 1. Correlation between NRBC count and birth weight

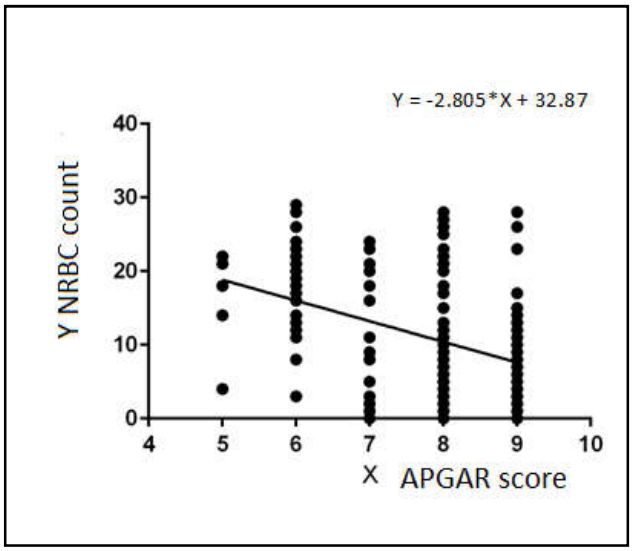

Fig.2. Correlation between NRBC count and APGAR score

DISCUSSION

In the present study, we have determined NRBC count/100 WBC in maternal and cord blood in normotensive and pre-eclamptic women to find association of NRBC count with perinatal outcome. The mean maternal NRBCs / 100 WBCs was 5.85 ± 4.022 in pre-eclamptic women as compared to 2.33 ± 2.571 in normotensive women, and the difference was statistically significant (P < 0.001). Our findings are in agreement with the study of Davari Tanha F[11], the maternal NRBC count was higher in pre-eclampsia group than in normotensive pregnant women (2.64 ± 1.23 v/s 0.44 ± 0.55), the difference was statistically significant (P < 0.009). Whereas Shripad Hebbar *et al*. (2014) observed that maternal NRBC count in pre-eclampsia Group was 2.4 ± 9.0 and Control group was 0.8 ± 1.5 but the difference was statistically not significant (P < 0.214). Aali *et al*. (2007) also reported a higher maternal NRBC in pre-eclamptic women than in normotensive women (2.70 ± 13.10 v/s 1.45 ± 14.20) but the difference was statistically not significant (P< 0.300). It has been suggested recently that the trafficking of fetal cells into the maternal periphery is disturbed in women with pre-eclampsia, which can result in elevation of NRBC in the maternal blood. The mean cord blood NRBCs in pre-eclamptic women was 16.19 ± 7.052 and in normotensive women was 5.41 ± 3.91 the difference was statistically significant (P < 0.001). Our findings are in concurrence with earlier studies conducted at different places and reported by different investigators. In the study of Aali *et al*. (2007), the mean cord blood NRBC count in normal pregnant women was 6.2 ± 8.1 compared to 18.2 ± 31.8 in pre-eclamptic group which was statistically significant. In the study of Sivakumar *et al*. (2007) the mean cord blood NRBC count in pre-eclamptic group was 7.38 compared to 1.72 in normotensive group, which was statistically significant. Shripad Hebbar *et al*. (2014) concluded that the mean cord blood NRBC count in pre-eclamptic group was 40.0 ± 85.1 and in normotensive group was 5.9 ± 6.3 which was statistically significant. Roya Faraji Darkhaneh *et al*. (2013) also found that the mean cord blood NRBCs was 11.12 ± 5.5 for newborns in the pre-eclampsia group and 2.74 ± 2.9 for newborns in the normotensive group (P < 0.05), which was statistically significant. It has been stated that the inability of cytotrophoblasts to differentiate correctly and subsequent failure to invade the uterus and its arterioles efficiently in pre-eclampsia lead to a relatively hypoxic placenta and a compensatory mechanism like enhanced production of nucleated RBCs is activated to counteract this imbalance. This results in increased NRBC count seen in cord blood of pre-eclamptic mothers. Mean cord blood NRBC count was higher in babies delivered by LSCS than those delivered vaginally. Mean cord blood NRBC count was significantly higher in babies having low APGAR score at 5 minutes. Nucleated red blood cell count showed an inverse relationship with APGAR scores at both 1 and 5 minutes. The exact mechanism causing the rapid release of NRBCs following acute asphyxia or precise time required to observe an increase in NRBC count is not known, although erythropoietin probably plays a major role in the process. Data from studies on animals (Widness *et al*., 1986; McMullin *et al*., 1988; Eckardt *et al*., 1989) and adults (Eckardt *et al*., 1989) suggest that erythropoietin increases within one to four hours of hypoxia. Elevated levels of cord blood erythropoietin have been found following acute birth asphyxia. (Maier *et al*., 1993; Ruth *et al*., 1990; Eckardt *et al*., 1990) Our study shows highly significant difference between NRBC counts of group with early neonatal mortality and group without neonatal mortality. According to various studies done by Phelan *et al*. (1995), Hanlon-Lundberg *et al*. (1999), Hermanser Mc. (2001), Beckers *et al*. (Hanlon-Lundberg *et al*., 1999), Ferns *et al*. (2004) and Darkhaneh *et al*. (2013), the elevated count of NRBCs in term neonates is related to hypoxemia, acidemia, asphyxia, lower Apgar scores, increased admission to NICU and increased neurologic injuries caused by asphyxia. According to Anil Kumar Mohanty *et al*. (2014) the

NRBC/100 WBC count was significantly higher in babies with adverse outcome, than the babies with good outcome, 65.44 (range 32-106) versus 42.14 (range 5-104) ($p < 0.001$). Similar results were observed in our study where mean cord blood NRBC count was more in babies having lower APGAR score, requiring neonatal admission or had perinatal mortality. Mean cord blood NRBC count has a direct relation with adverse perinatal outcome. Significant negative correlation was seen in cord blood NRBC count and birth weight and APGAR score. Our finding was in accordance with the finding observed by Colaco *et al*. (2014)

Conclusion

Elevated NRBC in the cord blood reflects fetal response to utero–placental insufficiency in pre-eclampsia. Cord blood nucleated red blood cells are significantly raised in preeclampsia and are associated with adverse early neonatal outcome. Neonates with elevated cord blood NRBC counts are more likely to have low birth weight, low APGAR score, neonatal ICU admission and perinatal mortality. Cord blood NRBC count is a simple and rapid test which is reasonably reliable, easy to perform and cost-effective. It can be done even at PHC level and provides valuable information about the well being of the newborn. The determination of NRBC count in cord blood can be used as an additional tool in the diagnosis of fetal asphyxia and predicting early perinatal outcome.

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