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Does Labor Affect Neonatal NRBC Count?

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ABSTRACT

Background & Objective: Nucleated red blood cells (NRBCs) enter the circulation in response to hypoxia, but it remains unknown how physiological delivery without fetal distress can change the NRBC level. Accordingly, in the present study, we compared the mean NRBCs per white blood cell (WBC) in the umbilical cord of normal vaginal delivery (NVD) with cesarean section (C/S). The present study was conducted to compare the mean NRBCs per WBC within umbilical cord in normal term newborns who were born by NVD with those delivered by C/S.

Materials & Methods: This case-control study was conducted for 305 neonates in two different groups, NVD (case) and C/S (control) groups. The blood samples were taken from umbilical veins to evaluate fetal NRBCs and WBC count after recording their demographic characteristics. Finally, all data were assessed using SPSS 16.

Results: The average age of mothers was 26.25±5.65 years. The average Apgar score of neonates was 8.23±0.6. The average NRBC count was 4.63±5.2. There was no significant difference in maternal age, parity, neonatal weight, and NRBC count per 100 WBCs between the two groups.

Conclusion: In the present study, the mean NRBC count within the umbilical cord of neonates born by elective C/S was less than those delivered by NVD, although this difference was not significant.

Keywords: Cesarean section, Nucleated red blood cell count, Newborn, Vaginal delivery

Introduction

Vaginal delivery is the preferred mode of delivery in most cases, but in many different clinical settings, cesarean section (C/S) might be prioritized (1). In cases that the vaginal birth might be dangerous for the mother or the fetus, C/S can help to save the mother or baby's life (2, 3). Compared with spontaneous vaginal delivery, C/S has practically higher surgical risks or subsequent prognosis. The cesarean delivery rate reached 32% in 2015 in the USA (4). In Iran, the prevalence of C/S is 48%, which is higher than the global average (5, 6). In many societies, C/S is so popular among women that more than half of them voluntarily prefer C/S (7). In Iran, one of the most important reasons for cesarean delivery on maternal request (CDMR) is fear of labor pain (8-11). In a study conducted in China, more than 66,000 participants, who were candidates for normal delivery and C/S, were assessed and compared according to outcomes.

It has been shown that the short-time rates of maternal and neonatal mortality are the same. However, respiratory distress syndrome rates are higher in the CDMR group (12). A smaller study compared these two modes of delivery and supported these findings (13). In the peripheral blood sample, nucleated red blood cells (NRBCs) are actually premature erythrocytes, increasing in response to elevated erythropoietin (EPO). The rise in the number of NRBCs in the neonatal circulation was associated with relative hypoxia and unfavorable outcomes (14, 15). Absolute NRBC amounts and NRBC percentage can be used as markers for predicting the neonatal mortality rate (16). To the

best of our knowledge, no research has examined the relationship between the NRBC count and delivery route. Therefore, the current study is considered to be a pioneer in this field.

Materials and Methods

This prospective observational case-control study was conducted in the Department of Obstetrics and Gynecology at Al-Zahra Maternity Hospital, which also serves as an educational center for undergraduate and postgraduate students of Guilan University, Rasht, Iran. Initially, the Institutional Ethical Committee approval was obtained. The study was conducted on 305 healthy full-term singleton newborns with a gestational age of 37 and 41 weeks and appropriated birth weight between February 2018 and November 2019. Gestational age was determined according to the last menstrual period (LMP) of the mother and confirmed with early pregnancy ultrasound. The birth weight was between 2.5 and 4 kg.

The following cases were not included in the study: preterm (gestational age<37 weeks), post-term (gestational age>42 weeks), intrauterine growth restricted (IUGR), and macrosomic neonates, as well as newborns with multiple anomalies and low birth weight (LBW), besides infants born from women with preeclampsia, diabetes, chorioamnionitis, and maternal chronic diseases. Further, neonates with perinatal infection, asphyxia, and meconium were also excluded from the study.

Normal NRBC was considered to be 10 or less, and abnormal NRBC was considered to be more than 10. The neonates were divided into two groups according to the mode of delivery. The first group consisted of 153 neonates (79 males [52%] and 74 females [48%]) born by normal vaginal delivery (NVD). The second group included 152 neonates (72 males [47%] and 80 females [53%]) delivered by elective C/S (repeated C/S, cephalopelvic disproportion CPD, breech, or transverse presentation). Venous umbilical cord blood was aspirated with a syringe from the double-clamped segment of the umbilical cord and transferred into an ethylenediaminetetraacetic acid (EDTA) tube.

Samples were sent to a laboratory, and a thin blood film was prepared on a glass slide, which was dried and stained with Leishman's stain. The slide was examined with an oil immersion lens to obtain a diff-erential white blood cell (WBC) count and calculate the number of NRBC in 100 WBCs. NRBCs were counted up to 500 WBCs with a cell counter and then reported as NRBC/100 WBCs. The correlation of umbilical cord blood, NRBC count, and final outcomes was evaluated and analyzed statistically. The Apgar score was evaluated immediately after birth and estim-ated twice, once at 1 and again at 5 minutes after childbirth.

Statistical Analysis

Data were analyzed using SPSS 20 (SPSS Inc., Chicago, Ill., USA), x2, and t test. The statistical significance was set at the 0.05 level.

Ethical Approval

This research was also approved by the Ethics Committee of Guilan University of Medical Sciences on 2020-07-01. This research was carried out under the financial support of Guilan University of Medical Sciences. The authors did not report any conflict of interest.

Results

The mean age of mothers was 26.25±5.65 years, ranging from 15 to 41. There was no significant statistical difference between the mean age of mothers in the two groups. The average gravidity was 1.57-±0.83 (min 1 and max 4), indicating no significant difference (*P*=0.191).

In the NVD group, 51.6% (79 cases) of newborns were male, and 48.4% (74 cases) were female; in the C/S group, 47.4% (72 cases) of newborns were male, and 52.6% (80 cases) were female. There was no significant difference between the two groups (*P*=0.456).

There was no significant difference in the mean level of umbilical cord hemoglobin (15.12±3.01; min 11.4 and max 18.9), but there was a significant difference in the mean level of postpartum maternal hemoglobin (13.41±2.41; min 8.9 and max 16.6) between the two groups according to Mann-Whitney *U* and chi-square tests. The mean duration of labor in the NVD group was 355.88±232.74 minutes (min 30 and max 900), bearing no significant relation to NRBC.

The median duration of rupture of membrane (ROM) in the NVD group was 338.85±234.44 minutes (min 30 and max 1020). The mean level of the first-minute Apgar score was 8.23±0.6 (min 7 and max 9). The average fifth-minute Apgar score was 9.1±0.49 (min 8 and max 10). There was no significant difference between the first- and fifth-minute Apgar scores in both groups using the Mann-Whitney *U* test (*P*=0.779 and *P*=0.08, respectively), but there was a significant difference between different Apgar scores in the NVD group (*P*=0.041). The mean neonatal weight at birth was 3336.16±373.79 g (min 2,500 g and max 4,000 g). There was a significant difference between the two groups (P=0.036).

The mean gestational age was 38.82±1.02 weeks (min 37 and max 41). The gestational age was significantly different between the two groups (P=0.-0001). The mean NRBC count was 4.63± 5.2 in both groups (min 0 and max 34). The mean WBC count was 41,000 (min 3,600 and max 41,600). The NRBC count was not significantly different between the two groups (P=0.087), but the mean WBC count was significantly higher in the NVD group (P=0.001; Table 1).

Table 1. Comparative study of maternal and neonatal demographic data as well as hematologic values of the two groups

Characteristics	NVD (N=153)	C/S (N=152)	*P
	M ± SD	M ± SD	
Age (yr)	26.12 ± 5.37	26.39 ± 5.93	0.938
Gravidity	1.46 ± 0.69	1.68 ± 0.94	0.055
Maternal hemoglobin (mg/dl)	14.22 ± 2.23	12.59 ± 2.31	0.0001
Gestational age (wk)	39.06 ± 1.04	38.57 ± 0.96	0.001
Birth Weight (gr)	3377.91 ± 386.5	3294.14 ± 357.2	0.036
APGAR (1 min)	8.21 ± 0.65	8.25 ± 0.51	0.775
APGAR (5 min)	9.21 ± 0.64	8.98 ± 0.21	0.08
WBC (n)	12515.69 ± 4877	10101.32 ± 3432	0.001
NRBC/ 100 WBC (n)	5.84 ± 5.99	4.4 ± 3.84	0.087

*Mann-Whitney

According to the chi-square test, there was no significant difference between the mean NRBC/100 WBCs for different ages, gestational ages, weights, and first-minute neonatal Apgar score. Only in the fifth-minute Apgar score, the mean NRBC/100 WBCs was significantly different (*P*=0.041; Table 2).

Table 2. Comparative study of maternal and neonatal charactristices of the two groups

Variable	Mode of delivery	Age group	Number	M±SD	*P
Age group (yr)	NVD	15-19	17	4.88±4.71	0.650
		20-24	39	6.17±5.72	
		25-29	60	5.31±6.3	
		30-34	24	6.58±6.64	
		35<	13	7.23±5.96	
	C/S	15-19	12	3.33±4.18	0.396
		20-24	60	3.25±3.3	
		25-29	34	3.32±4.7	
		30-34	24	2.83±3	
		35<	22	4.63±4.57	
Parity	NVD	1	100	6.12±6.26	0.599
		2	37	5±5.29	
		3≤	16	6.12±5.94	
	C/S	1	84	3.32±3.77	0.694
		2	46	3.5±4.26	
		3≤	22	3.54±3.46	
Sex	NVD	male	79	6.92±6.88	0.074
		female	74	4.7±4.64	
	C/S	male	72	3.12±2.73	0.485
		female	80	3.66±4.56	
Gestational Age (Week)	NVD	37-(38+6)	47	4.91±4.22	0.850
		39-(40+6)	99	6.07±6.33	
		41	7	9±9.91	

Variable	Mode of delivery	Age group	Number	M±SD	*P
Fetal weight (g)	C/S	37-(38+6)	80	3.23±4.10	0.196
		39-(40+6)	70	3.64±3.64	
		41	2	2±0	
	NVD	2500-2999	29	3.96±3.24	0.385
		3000-3499	72	5.51±5.04	
		3500-4000	52	7.36±7.83	
	C/S	2500-2999	39	2.51±1.89	0.248
		3000-3499	74	3.43±4.29	
		3500-4000	39	4.25±4.34	
1st.min APGAR Score	NVD	7	20	8.4±6.49	0.07
		8	81	5.79±6.03	
		9	52	4.96±5.55	
	C/S	7	6	1.16±0.75	0.106
		8	102	3.71±4.26	
		9	44	3±2.91	
5th. min. APGAR Score	NVD	8	19	8.78±6.42	0.041
		9	83	5.65±5.98	
		10	51	5.01±5.61	
	C/S	8	5	3±2.54	0.968
		9	145	3.41±3.91	
		10	2	4±4.24	

*Mann-Whitney

Discussion

Of the 305 women enrolled in this study, 153 had a vaginal delivery, and 152 had C/S. Most mothers were between 20 and 29 years old. The majority of subjects in the NVD group (63/8% cases) were in the age range of 20 to 29 years, and most subjects in the C/S group (60.6% of cases) were in the age range of 20 to 24 years. Accordingly, it was confirmed that younger mo-thers were more willing to have C/S. However, there was no significant relationship for the distribution of age range. Maternal gravidity was between 1 and 6, and the majority of NVDs and C/Ss were related to primary paresis. The normal NRBC (≤10) was 47.4% (127 cases) in the NVD and 52.6% (141 cases) in the C/S group.

The abnormal NRBC (>10) was 70.3% (20 cases) in the NVD group and 29.7% (11 cases) in the C/S group. Of all subjects, 268 (87.86%) had normal NRBCs, and 37 (12.13%) had abnormal NRBCs. One of the reasons for the high C/S rate in primi-paresis against the multi-paresis - was their own choice. According to our study, there was no relationship between the average labor duration (from active phase to delivery) and the NRBC count.

Our finding was similar to the results of the Qaiser's and Redzeko's study, presenting the effects of natural labor occasionally exacerbated by NRBC **(17, 18)**. The first- and fifth-minute Apgar scores were in the range of 7 to 10 (mostly 9) in both vaginal delivery and C/S groups. Further, there was a significant relationship between the fifth-minute Apgar scores in both groups (P=0.08).

Hanlon-Lundberg and colleagues found no signi-ficant relationship for the neonatal Apgar score in both modes of delivery. In this study, 61.03% of neonates had the Apgar score of 7-10. The birth weight of newborns was 2.5-4 kg. Most newborns weighed more than 3 kg. The weight was 3-3.5 kg in 54.5% of new-borns in the C/S group and 55.6% of newborns in the NVD group. The results of our study were similar to Hanlon-Lundberg et al.'s study. There was no signi-ficant relationship for the average number of NRBCs in both two studies (P=0.008). It was confirmed that the mode of delivery did not affect the amount of NRBC **(19)**.

Thilaganathan showed that the weight range in both groups was similar. In this study, the mean gestational

age was 40 and 38 weeks in the NVD and C/S groups, respectively **(20)**.

McCarthy concluded that the stress of uncomplicated NVD did not increase the blood flow to the fetus umbilical cord **(21)**. In a study by Vatansever, the number of NRBCs in the NVD group was significantly different from the C/S group (P=0.002), indicating the effect of delivery mode on the NRBC count **(22)**.

Similar to Redzeko's study, we can conclude that there was no statistically significant relationship between the duration of labor and the NRBC count. This might indicate that physiological labor stress has no effect on NRBC. The mean hemoglobin of the mother's blood was 13.41±2.41. The mean hemoglobin of the cord in both groups was significantly different from Redzeko's study (P=0.0001; max 18.9 and min 11.4) **(18)**. The mode of delivery can affect WBC, RBC, NRBC, hematocrit, and hemoglobin. In a statistical study, no statistically significant difference was observed between the number of NRBCs per 100 WBCs in different age groups (PC/S=0.396, PNVD=0.65), parity (PC/S=0.694, PNVD=0.599), neonatal sex (PNVD=0.074, PC/S=0.485), pregnancy weeks (PC/S=0.196, PNVD=0.850), and the first-minute Apgar (PNVD=0.07, PC/S=0.106); however, a statistically significant difference was observed in the fifth-minute Apgar score (PC/S=0.968, PNVD=0.041).

On the other hand, there was no significant relationship between NRBC per 100 WBCs of different weights in the NVD group, but this relationship was significant in the C/S group (P=0.0001). In a study by Sheffer, there was no significant relationship between NRBC, parity, maternal age, gestational age, and fetal gender. Also, it was concluded that physiological delivery did not cause fetal hypoxia. On the other hand, hypoxia was not long enough to cause hematologic manifestations due to increased erythropoietin **(23)**.

Manegold et al. showed that the number of NRBCs per 100 WBCs in C/S following fetal distress was significantly higher than in the case of unsuccessful labor and elective C/S (P<0.05). This result indicates an increase in NRBC counts following fetal distress **(24)**. Further, Paamoni claimed that babies born by C/S were more likely to be exposed to oxidative stress than babies born by NVD **(25)**.

Thorkelsson et al. claimed that NRBC in the umbilical cord of newborns born by NVD was higher than those born by C/S, and the rate of oxygen delivery to the fetus was lower in the NVD group **(26)**. The results of these two studies contradict our results because there was no significant relationship between the mode of delivery and the number of NRBCs. In our study, no increase was observed in the NRBC of the umbilical cord in the NVD group; this indicates that no fetal distress is created with NVD. As a result of substituting C/S for normal delivery in problem-free births, the occurrence of fetal distress was unlikely and unreasonable.

Besides, the stress caused by NVD is not enough to produce complications generated by fetal distress. However, according to our results, the average NRBC in the umbilical cord of infants born by C/S was lower than those born by NVD, but this difference was not statistically significant. However, the process of natural delivery is considered to be a possible cause of this difference.

Conclusion

Term infants born by uncomplicated NVD had a higher cord NRBC count at birth than those born by elective C/S, but this difference was not significant.

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Conflict of Interest

The authors declared no conflict of interest.

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