Significance of high and normal neonatal nucleated red blood cell count in small-for-gestational-age newborns

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Summary

The objective of this study was to evaluate the obstetrical and neonatal outcome in small-for-gestational age (SGA) and appropriate-for-gestational-age (AGA) fetuses with normal and elevated neonatal nucleated red blood cell counts. Therefore the nucleated red blood cell count was assessed immediately after birth in 906 neonates delivered at our institution and the perinatal and neonatal data were compared. Postnatally, infants were classified as SGA if they had a birth weight for given gestational age below the 10th percentile. Neonates were allocated to four groups according to their nucleated red blood cell count: SGA neonates with normal and high nucleated red blood cell count and appropriate-for-gestational-age newborns (AGA) with normal and high nucleated red blood cell count. Statistical analysis included the Mann-Whitney U-Test, Student's t-test, χ^2 analysis of variance and stepwise regression analysis. SGA newborns with high nucleated red blood cell count had a significantly lower birth weight, a lower gestational age at delivery, lower arterial and venous pH values, lower Apgar scores at 1 min, 5 min and 10 min as well as lower base excess values compared to the other groups. They had to be transferred significantly more often and stayed longer in the neonatal intensive care unit. Three cases of intraventricular hemorrhage, four cases of necrotizing enterocolotis and two neonatal deaths occurred all in the SGA group with high neonatal nucleated red blood cell counts. Neonatal outcomes of SGA and AGA newborns with normal nucleated red blood cell counts were comparable. Our data do therefore underline the possible value of neonatal nucleated red blood cell counts to differentiate the healthy small-for-gestational age newborn from the truely growth retarded newborn.

Key words: Small-for-gestational-age; Intrauterine growth retardation,; Nucleated red blood cell count; Perinatal outcome.

Introduction

Nucleated red blood cells are immature erythrocytes and are not an uncommon finding in the circulating blood of newborns [1, 2]. Their presence was noted as early as 1941 by Anderson [3]. Red blood cell production depends on the stimulation of erythropoietic stem cells by erythropoietin. Because erythropoietin does not cross the placenta, elevated erythropoietin concentrations in fetal cord blood in cases of hypoxemia are of fetal origin. Elevated counts of nucleated red blood cells have been suggested to be associated with intrauterine hypoxemia and adverse neurologic outcome in newborns [4, 5]. Generally up to 8 nucleated red blood cells per 100 white blood cells are found in the circulation of healthy term neonates [6-8]. Conditions related to increased nucleated red blood cell counts are maternal diabetes mellitus, prematurity, intrauterine growth retardation and Rh sensitization [4, 6, 7]. Furthermore, we previously reported on slightly elevated numbers of nucleated red blood cells in post-term fetuses possibly reflecting altered fetal oxygenation under these circumstances [8, 9].

There have been numerous studies dealing with the correlation of abnormal umbilical Doppler velocimetry with adverse perinatal outcome in selected populations [10-13]. Fetal adaption to severe intrauterine hypoxemia is known to be associated with an absent or reversed flow in the fetal aorta or umbilical artery and subsequent centralization of the fetal circulation detected by Doppler studies [14, 15]. The association of high counts of neonatal nucleated red blood cells and increasing Doppler pathology in the fetoplacental unit has been reported previously by us and other groups [16-20]. Furthermore, as an end-point of Doppler pathology, abnormal venous flow velocity waveforms have been reported to be associated with severe intrauterine hypoxemia [20].

There is a large body of evidence suggesting that the intrauterine growth retarded fetus is at greater risk for adverse perinatal outcome including fetal asphyxia and long term neurologic impairment [21-26]. On the other hand, not necessarily all newborns with a birth weight below the 10th percentile for gestational age may have suffered from intrauterine growth retardation but may just be small-for-gestational age (SGA) and otherwise healthy. Previously, Minior *et al.* reported on the possible value of nucleated red blood cell counts to distinguish between growth retarded and small-for-gestational-age fetuses in a smaller series [27].

Additionally, there is increasing evidence that hypoxic-ischemic injury of the growth retarded newborn might not be related to labor, but may have occurred before during intrauterine life [28-31]. For example, clinical or biochemical indicators of severe fetal asphyxia are found in only 10% to 20% of cerebral palsy cases [29].

Thus the search for markers for intrauterine hypoxemia which could help to differentiate truely growth retarded newborns from healthy small-for-gestational-age new-

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borns remains an important and relevant task of modern perinatal medicine and has important medico-legal aspects.

The purpose of the study presented was to compare the perinatal and neonatal data of small-for-gestational-age newborns and appropriate-for-gestational-age newborns with high and normal nucleated red blood cell counts.

Material and Methods

This prospective study was undertaken in the Department of Obstetrics and Prenatal Ultrasound at the University Hospital of the Saarland after informed consent was obtained from all women. Multiple pregnancies, chorioamnionitis, maternal renal disease, maternal diabetes, maternal cardiovascular pathology other than hypertension and fetuses with chromosomal or structural anomalies were excluded from evaluation.

Immediately after delivery a blood sample was drawn from the umbilical artery and vein by needle aspiration. NRBC count was assessed from the umbilical artery sample. Two blood smears of each sample stained with Wright's stain were prepared, and the number of NRBCs per 100 WBCs was assessed by light microscopy by two trained observers who were blinded for the study groups. According to our own institutional reference ranges a nucleated red blood cell count > 90th percentile for gestational age was considered as elevated. Subsequently the neonates were allocated to four study groups on the basis of their nucleated red blood cell count and their birth weight; 906 neonates with a complete nucleated red blood cell count were enrolled into the study and allocated to four study groups (Table 1). The estimated time of delivery was assessed by last menstrual date and a vaginal ultrasound measurement of the crown-rump length within the first 12 weeks after the last menstruation. SGA was defined as a birth weight < 10th percentile for gestational age of our locally used growth charts [32]. Histologic chorioamnionitis was diagnosed by the presence of acute inflammatory cell infiltration of both layers of the membranes. Prematurity was defined as delivery before 37 completed weeks of gestation.

Table 1. — *Study groups according to the nucleated red blood cell count.*

Group 1 n=179	small-for-gestational-age-neonates with normal nucleated red blood count
Group 2 n=67	small-for-gestational-age-neonates with high nucleated red blood cell count
Group 3 n=571	appropriate-for-gestational-neonates with normal nucleated red blood cell count
Group 4 n=89	appropriate-for-gestational-age-neonates with high nucleated red blood cell count

Outcome measures included nucleated red blood cell counts, birth weight, gestational age at delivery, arterial and venous pH, arterial base excess, Apgar score, admission to the neonatal intensive care unit, length of stay in the neonatal intensive care unit, duration of mechanical ventilation, incidence of intraventricular hemorrhage, incidence of necrotizing enterocolitis and neonatal death.

The results were analyzed with the SPSS statistical software (SPSS Inc., Chicago, IL, USA). Distribution of nucleated red blood cells was non-normal. Neonatal nucleated red blood cell counts are presented as median and range, otherwise mean ±SD was used. Statistical analysis included the Mann-Whitney U-Test, Student's t-test, χ^2 analysis of variance and stepwise regression analysis. Bonferroni correction for multiple testing was used. A p-value < 0.05 was considered to indicate a significant difference.

Results

In this study we included 906 neonates with a complete neonatal blood cell count who were delivered at the University Hospital of Homburg/Saar from July 1998-June 2000. Two-hundred and forty-six newborns were SGA (27%) and 660 (73%) newborns were AGA. The obstetrical and perinatal data of the four study groups are given in Table 2 and the cord blood values with the Apgar scores are shown in Table 3.

SGA neonates with high nucleated red blood cell counts presented significantly lower arterial and venous pH values compared to all other groups (pH 7.24 ± 0.10, $p < 0.01$, $p < 0.001$, Table 3) as well as the lowest Apgar scores after 1 min, 5 min and 10 min (6.58 ± 2.21; 8.42 ± 1.26; 8.34 ± 2.47, $p < 0.01$, respectively, Table 3). The neonates in group 2 more frequently presented Apgar

Table 2. — *Obstetrical and perinatal outcomes*

	Group 1 n = 179	Group 2 n = 67	Group 3 n = 571	Group 4 n = 89	Statistical significance
Gest. age at delivery, weeks	37.2±3.0 [27.7–41.8]	33.1±3.9 [26.5–40.7]	39.4±1.5 [29.4–42.1]	37.8±3.6 [27.9–41.6]	p<0.001*, p<0.01‡, p<0.001#, p<0.05†
Birth weight, grams	2389±502	1561±752	3379±446	3192±856	p<0.001*, p<0.001‡, p<0.001#
Preterm delivery	61 (34.1%)	49 (73.1%)	26 (4.6%)	24 (27%)	p<0.01*, p<0.001‡, p<0.001#, p<0.01†
Vaginal delivery	104 (58.1%)	17 (25.3%)	471 (82.4%)	64 (71.9%)	p<0.01*, p<0.01‡, p<0.001#
Cesarean delivery	75 (41.9%)	50 (74.7%)	100 (17.6%)	25 (28.1%)	p<0.01*, p<0.05‡, p<0.01#, p<0.05†
NICU admission	89 (49.7%)	59 (88.1%)	37 (6.5%)	32 (36.0%)	p<0.001*, p<0.001‡, p<0.001#, p<0.001†
Duration of NICU stay, days	24.9 [4–58]	41.5 [6–89]	12.6 [1–68]	29.0 [3–77]	p<0.05*, p<0.001‡, p<0.05†
Need for mechanical ventilation, days	0.6 [0–7]	2.9 [1–11]	0.3 [0–3]	1.6 [0–11]	p<0.05*
Intraventricular hemorrhage (I°-IV°)	0	3 (3.4%)	0	0	
Necrotizing enterocolitis	0	4 (5.9%)	0	0	
Neonatal mortality	0	2 (2.9%)	0	0	

*group 1 vs. group 2, ‡ group 1 vs. group 3, # group 2 vs. group 4, † group 3 vs. group 4. Data are presented as mean ± SD with range in parentheses or numbers with percentage of group or range in parentheses.

Table 3. — *Cord gas values and Apgar scores.*

	Group 1 n = 179	Group 2 n = 67	Group 3 n = 571	Group 4 n = 89	Statistical significance
NRBC/100WBC	7 [0-15]	31 [16-720]	2 [0-8]	13 [9-201]	
Arterial pH	7.28±0.07	7.24±0.10	7.29±0.06	7.27±0.08	p<0.01*, p<0.05‡, p<0.01#, p<0.05†
Venous pH	7.33±0.08	7.29±0.07	7.35±0.06	7.34±0.08	p<0.01*, p<0.01‡, p<0.001#
Arterial base excess, mmol/l	–4.1	–4.7	–4.1	–5.0	p<0.5*, p<0.05†
	[-14.0–1.8]	[-18.7–3.7]	[-13.1–1.7]	[-20–1.8]	
Apgar score at 1 min	7.6 [1–10]	6.5 [1–9]	8.7 [3–10]	7.9 [1–10]	p<0.001*, p<0.001‡, p<0.01#, p<0.05†
Apgar score at 5 min	8.9 [4–10]	8.4 [3–10]	9.6 [5–10]	9.0 [4–10]	p<0.01*, p<0.001‡, p<0.01#, p<0.05†
Apgar score at 10 min	9.1 [6–10]	8.3 [5–10]	9.7 [7–10]	8.9 [5–10]	p<0.001*, p<0.001‡, p<0.01#, p<0.05†
Apgar score <7 at 5 min	20 (11.1%)	10 (15.0%)	18 (3.2%)	13 (14.6%)	p<0.01*, p<0.001‡, p<0.001†
Apgar score <7 at 10 min	12 (6.7)	10 (15.0%)	10 (1.8%)	11 (12.4%)	p<0.001*, p<0.01‡, p<0.001†
Arterial pH <7.20	20 (11.2%)	11 (16.4%)	38 (6.7%)	12 (13.5%)	p<0.01*, p<0.01‡, p<0.05#, p<0.01†
Venous pH <7.20	7 (3.9%)	9 (13.4%)	9 (1.6%)	5 (5.6%)	p<0.001*, p<0.001#, p<0.05†
Arterial base excess < –8 mmol/l	15 (8.4%)	9 (13.4%)	36 (6.3%)	14 (15.7%)	p<0.01*, p<0.01†

group 1 vs. group 2, ‡ group 1 vs. group 3, # group 2 vs. group 4, † group 3 vs. group 4; Data are presented as mean ± SD with range in parentheses or numbers with percentage of group or range in parentheses.

scores < 7 after 5 min and 10 min (except for group 4), arterial and venous pH values < 7.20 as well as arterial base excess values < –8 mmol/l (except for group 4) compared to all other groups ($p < 0.01$, $p < 0.001$, Table 3). Furthermore they had to be transferred significantly more often to the neonatal intensive care unit (88%, $p < 0.01$) than newborns of the other groups and the length of stay in the neonatal intensive care unit was the longest among all study groups (mean 41.5 days, range 6-89 days, Table 2, except for group 4). SGA newborns with high nucleated red blood cell counts needed significantly longer mechanical ventilation than the SGA newborns with normal nucleated red blood cell counts (mean 2.9 days, range 1-11 days, Table 2). We observed three cases of intraventricular hemorrhage (3.4%), four cases of necrotizing enterocolitis (5.9%) and two neonatal deaths (2.9%) in our series, all of them occurring in the group of SGA newborns with high nucleated red blood cell counts. These incidences in the group of SGA newborns with high nucleated red blood cell counts did not reach statistical significance probably due to the small numbers.

Stepwise regression revealed that a high nucleated red blood cell count was the strongest predictor of adverse perinatal outcome followed by gestational age at delivery and birth weight.

Subgroup analysis between SGA newborns with normal and high nucleated red blood cell counts revealed significantly lower arterial pH, venous pH, arterial base excess values as well as lower Apgar scores in the latter group ($p < 0.001$, respectively). Those SGA newborns with high nucleated red blood cell counts had to be transferred more often to the neonatal intensive care unit (88% vs. 49%, $p < 0.01$) had to stay significantly longer in the neonatal intensive care unit (41.5 days vs. 24.9 days, $p < 0.05$) and were significantly more likely to require longer mechanical ventilation (2.9 days vs. 0.6 days, $p < 0.05$).

With regard to AGA neonates with normal nucleated red blood cell counts SGA neonates with normal nucleated red blood cell counts revealed significantly lower values for arterial and venous pH as well as for the Apgar scores. However, there were no differences between these two groups with respect to the length of mechanical ventilation, the incidence of intraventricular hemorrhage, the incidence of necrotizing enterocolitis or the neonatal mortality rate.

Discussion

The results of this study demonstrate that elevation of nucleated red blood cell counts in SGA neonates is associated with adverse short-term perinatal outcome. In contrast, the outcome of SGA neonates with normal nucleated red blood cell counts was basically comparable to the outcome of AGA fetuses with normal nucleated red blood cell counts. These findings are in good accordance with recent studies of Minior *et al.*, showing higher morbidity and mortality rates in SGA fetuses with high nucleated red blood cell counts [27]. We attempted in a large series to differentiate the healthy small-for-gestational-age fetus from the fetus who suffered from intrauterine growth retardation by assessing the nucleated red blood cell count after birth. Recently, we have, among others, demonstrated increasing nucleated red blood cell counts to be associated with abnormal fetal Doppler studies and adverse perinatal and neonatal outcome in growth retarded fetuses [16-20].

Modern perinatal medicine has contributed to an important reduction of perinatal mortality over the last three decades from about 3% to 0.5%-0.6% according to the perinatal data base in Germany [29, 33]. Conversely, a comparable reduction of perinatal neurologic morbidity was not observed. In Germany about 1,000 children per year are still born with a cerebral hypoxic-ischemic injury and bilateral cerebral palsy is found in 2/1,000 livebirths [29, 33].

For many years cerebral hypoxic-ischemic injury of the newborn has been attributed to intrapartum asphyxia. During the past several years, however, it has become

evident that long-term neurologic impairment of the neonate might not be primarily due to intrapartum asphyxia, but, rather, might occur long before during intrauterine life. In addition, in only in 10%-20% of cases of cerebral palsy has an association with clinical or biochemical markers of fetal asphyxia been observed [28-31].

Fetal erythropoiesis is mainly driven by the hypoxia-erythropoietin-nucleated red blood cell precursors [34].

Elevated nucleated red blood cell counts have been proposed by previous studies as a marker of intrauterine hypoxemia in term infants [6, 7].

Kors *et al.* reported on distinct nucleated red blood cell patterns in relation to the timing of fetal injury in neurologically impaired neonates. They found higher nucleated red blood cell counts in cases with suspected injury before admission to the hospital than in cases with injury occurring acutely during birth. Korst *et al.* concluded that nucleated red blood cell levels may assist in determining the timing of fetal neurologic injury [5]. Phelan *et al.* found in their series of 46 singleton term neurologically impaired neonates that the number of NRBCs was lower when fetal asphyxia occurred closer to birth [4]. Therefore the number of nucleated red blood cells at birth should aid in determining the time of fetal asphyxia.

Is an animal model release of reticulocytes after hypoxia was not seen until the second or third day after the hypoxic stimulus [35]. Given this observation, elevated NRBC counts should be found in the cord blood of the neonate only if the hypoxic insult occurs before the onset of labor. Therefore elevated NRBC counts after acute intrapartum hypoxia are not expected in the postpartum cord blood, but might result in elevated counts during the neonatal period. This is in accordance with our previous work which did not show any relation between mode or duration of delivery and nucleated red blood cells in uncomplicated term and post-term pregnancies [8].

However, chronic intrauterine hypoxemia and acidemia may also alternatively result in dysfunctional fetal erythropoiesis with subsequent anemia or pancytopenia. This fact has recently been underlined by findings of Baschat and co-workers. In their series of growth retarded fetuses they found the highest nucleated red blood cell counts not to be associated with higher hematocrit and hemoglobin values. The authors therefore concluded, that the interrelationship of hypoxemia, erythropoietin release, and nucleated red blood cell production and release remains unclear [19]. Furthermore, Mladenovic *et al.* have suggested modulation of erythropoiesis by epinephrine, an acute stress hormone [36].

In conclusion, an increased nucleated red blood cell count might become an additional valuable tool, together with the Doppler flow, in the differentiation of growth retarded neonates from the healthy, but small-for-gestational-age newborn. However, further studies are required to get further insight into the hypoxemia-erythropoietin-NRBC axis and the neonatal red blood cell count of small-for-gestational-age and intrauterine growth retarded newborns.

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