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Neonatal Hemoglobin Levels in Preterm Infants Are Associated with Early Neurological Functioning

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Keywords
Neonatal anemia · Preterm infants · General movements · Neurological functioning

Abstract
Background: Neonatal anemia may compromise oxygen transport to the brain. The effects of anemia and cerebral oxygenation on neurological functioning in the early neonatal period are largely unknown. ***Objective:*** This study aimed to determine the association between initial hemoglobin levels (Hb) and early neurological functioning in preterm infants by assessing their general movements (GMs). ***Methods:*** A retrospective analysis of prospectively collected data on preterm infants born before 32 weeks of gestation was conducted. We excluded infants with intraventricular hemorrhage > grade II. On day 8, we assessed infants' GMs, both generally as normal/abnormal and in detail using the general movement optimality score (GMOS). We measured cerebral tissue oxygen saturation (r_cSO_2) on day 1 using near-infrared spectroscopy. ***Results:*** We included 65 infants (median gestational age 29.9 weeks [IQR 28.2–31.0]; median birth weight 1,180 g [IQR 930–1,400]). Median Hb on day 1 was 10.3 mmol/L (range 4.2–13.7). Lower Hb on day 1 was associated with a higher risk of abnormal GMs (OR = 2.3, 95% CI: 1.3–4.1) and poorer GMOSs (B = 0.9, 95% CI: 0.2–1.7). Hemoglobin strongly correlated with r_cSO_2 (rho = 0.62, p < 0.01). Infants with lower r_cSO_2 values tended to have a higher risk of abnormal GMs (p = 0.06). After adjusting for confounders, Hb on day 1 explained 44% of the variance of normal/abnormal GMs and r_cSO_2 explained 17%. Regarding the explained variance of the GMOS, this was 25% and 16%, respectively. ***Conclusions:*** In preterm infants, low Hb on day 1 is associated with impaired neurological functioning on day 8, which is partly explained by low cerebral oxygenation.

Introduction

Neonatal anemia is common in preterm infants. Anemia may induce tissue hypoxia, possibly resulting in cell injury. Red blood cell (RBC) transfusions aim to rapidly improve oxygen transport to vital organs. Up to 60% of preterm infants born before 32 weeks of gestational age (GA) receive RBC transfusions for anemia, mainly as a result of iatrogenic phlebotomy loss and when ventilatory support is required to improve oxygen delivery [1]. Ane-

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mia and RBC transfusions are strongly related during the first days after birth [2] and are associated with mortality and short-term morbidity, such as hemodynamic significant patent ductus arteriosus (PDA) and intraventricular hemorrhage (IVH) [2, 3].

Severe neonatal anemia leads to decreased oxygen transport and decreased oxygenation in the brain [4]. This is associated with adverse effects on maturation of the central nervous system and subsequent neurodevelopment [5]. Conversely, RBC transfusions increase cerebral tissue oxygenation, which may benefit infants' neurological condition [6]. Transfusions could, however, also induce oxidative stress and subsequent neuronal injury. Contradictory results were published on long-term outcomes in infants treated according to either liberal or restrictive RBC transfusion guidelines during neonatal intensive care unit (NICU) stay [7, 8]. Early neurological assessment may bring to light the underlying pathophysiological mechanisms.

The effects of anemia and cerebral oxygenation on neurological functioning in the early neonatal period are largely unknown. A widely applied method to monitor cerebral tissue oxygen saturation (r_cSO_2) in neonates is near-infrared spectroscopy (NIRS). Cerebral oxygenation measures can also serve as a prognostic tool for predicting outcomes in preterm infants [6, 9]. A reliable and valid tool to determine neurological functioning in young infants is Prechtl's method of general movement assessment (GMA) [10, 11]. The quality of general movements (GMs), combined with detailed aspects of these movements as reflected in the general movement optimality score (GMOS), is of significant diagnostic value in preterm infants [12, 13], with fair to good prognostic value after the first postnatal week [14].

The aim of our study was to determine the association between initial hemoglobin levels (Hb) and GMA on day 8 after birth in preterm infants born before 32 weeks of gestation. We hypothesize that low Hb and its concomitant low cerebral oxygenation is independently associated with poorer neurological functioning.

Methods

Study Design and Participants

We performed a retrospective analysis on prospectively collected data on inborn and outborn preterm infants admitted to the NICU of the University Medical Center Groningen (UMCG) between May 2006 and April 2018. They were either part of a previously published prospective observational study [6, 15] or a recent unpublished observational pilot study on the feasibility of adding early GMA to standard NICU in all preterm born infants ≤30 weeks of gestation. Inclusion criteria of the previous 2 trials were GA <32 weeks in one of them [6] and fetal growth restriction defined as fetal abdominal circumference or estimated fetal weight <10th percentile or declining fetal growth ≥30 percentiles in the other [15]. Both studies were approved by the UMCG Medical Ethics Review Board.

Infants were eligible for the current study if they met the following criteria: GA ≤32 weeks and a video recording of GMs on day 8 after birth. We excluded infants with chromosomal abnormalities or if they were diagnosed with an IVH > grade II, according to Papile's classification, to prevent inclusion of cases where abnormal GMs were a result of severe IVH. Transfusion thresholds were according to the Dutch anemia transfusion protocol (online suppl. Table 1; see www.karger.com/doi/10.1159/000518655 for all online suppl. material).

Video Recordings and Movement Optimality Scores

Our primary outcome was the quality of GMs, including detailed scoring, on day 8. This was obtained from a 45-min video recording, in accordance with Einspieler and Prechtl [11]. Because from the end of the first week onward GMA is reliable with even a moderate prognostic value [14], we assessed the neurological condition on day 8, being close to the risk factor of interest, that is, Hb on day 1. The infant was laid in the supine position, wearing only a diaper. Recordings during crying, fussing, hiccupping, or sucking on a pacifier were excluded from analyses [11]. All recordings were evaluated offline by 2 researchers (W.S.K. and A.F.B.). We first categorized the GMs into normal, poor repertoire, cramped-synchronized, or chaotic GMs [11]. Subsequently, we scored their detailed characteristics using the GMOS. The first part of the GMOS refers to the general GM categories. The second part focuses on detailed scoring of the neck and trunk and upper and lower extremities, separately. The GMOS results from adding the scores of the 3 categories plus the score for general quality. A score of 42 indicates the best possible performance and 5 the poorest [12]. In case of absent or only very brief GMs (<3 s), the infant was classed as hypokinetic, and a GMOS was not performed.

Clinical Variables

Hemoglobin on day 1 was retrieved from the infants' medical records. From these records, we also collected other clinical data including GA, birth weight (BW), Hb on day 8, the RBC transfusions administered, Apgar score, illness severity assessed according to the Score for Neonatal Acute Physiology-Perinatal Extension II (SNAPPE-II) [16], presence of a PDA, and mechanical ventilation.

We measured r_cSO_2 using NIRS, a noninvasive procedure, and used the INVOS 5100 c oximeter in combination with neonatal sensors (Medtronic, Dublin, Ireland). The sensor was placed on either the left or right side of the infants' forehead. We calculated mean r_cSO_2 of a 2-h recording on day 1, in which the correct sensor position was documented. We used the mean r_cSO_2 obtained for each individual infant for analyses.

Statistical Analyses

We used SPSS version 23.0 (IBM Corp., Armonk, NY, USA) for statistical analyses. Patient characteristics were described as median interquartile range (IQR) or number (*n*) percentage. Using Pearson's correlation test, we calculated the correlation coefficient between infants' Hb on day 1 and r_cSO_2. Next, we calculated odds ratios and 95% confidence intervals for abnormal GMs. We also

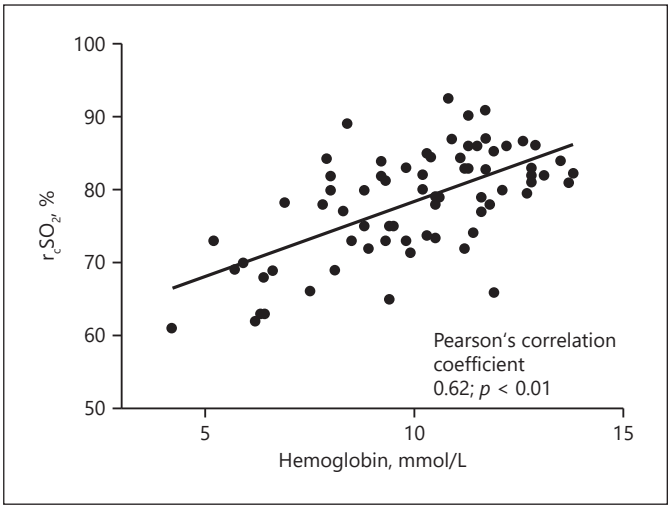

Fig. 1. Relation between hemoglobin level and cerebral tissue oxygen saturation on day 1. r_cSO_2, cerebral tissue oxygen saturation.

performed linear regression analyses to test whether Hb on day 1, Hb during video recording on day 8, and cerebral oxygenation were predictive of GMOS. The potential confounders we considered were infants' year of birth, GA, Apgar scores, illness severity, and whether they were born small-for-gestational age (SGA). These factors, which were univariately associated with either abnormal GMs or GMOS at $p < 0.20$, were included in multiple regression models, taking the potential influence of multicollinearity into account. Statistical significance was defined as $p < 0.05$.

Because our cohort had a fixed number of infants, we were hesitant to perform a power analysis. Nevertheless, we calculated how many infants we required for this study to make a meaningful conclusion. Regarding the association between GMOS and Hb on day 1, we considered a correlation coefficient of 0.4 as relevant. With a power of 0.8 and alpha 0.05, we needed to include 43 infants or 61 infants if we would include 2 covariates in the analyses.

Results

Participants and Video Recordings

We included 65 infants with a median GA of 29.9 weeks (IQR 28.2–31.1) and a median BW of 1,180 g (IQR 930–1,403). Of them, 46 were born between 2006 and 2007, 16 between 2012 and 2014, and 3 in 2018. Median Hb on day 1 was 10.3 mmol/L (range 4.2–13.7). Median r_cSO_2 on day 1 was 80% (IQR 73–84). Twenty infants (31%) received an RBC transfusion before day 8. Hemoglobin on day 8 ranged from 6.1 to 12.5 mmol/L. Baseline characteristics are depicted in Table 1.

In Table 2, we present the classification of the quality of the GMs and the GMOSs. Seven infants were classed as hypokinetic on account of sepsis. The GMOS was as-

Table 1. Patient characteristics

	Median (range) or *n* (%)
Gestational age, weeks	29.9 (26.0–31.9)
Birth weight, g	1,180 (560–2,250)
SGA	36 (55)
LGA	6 (9)
Sex, male	26 (40)
Apgar score at 5 min	8 (3–10)
SNAPPE-II	14 (5–39)
Hemoglobin, mmol/L	
On day 1	10.3 (4.2–13.7)
On day 8	8.4 (6.1–12.5)
r_cSO_2 on day 1, %	80 (61–91)
Infants with r_cSO_2 below 72% on day 1	12 (18)
RBC transfusion received	34 (52)
Before day 8	20 (31)
Mechanical ventilation [a]	42 (65)
On day 8	8 (12)
Treatment with inotropes[b] on day 1	8 (12)
PDA[c]	22 (34)
IVH grades I–II	10 (15)
Survival during NICU stay	59 (91)

SGA, small-for-gestational age (<10th percentile); LGA, large-for-gestational age (>90th percentile); SNAPPE-II, score for neonatal acute physiology-perinatal extension II; r_cSO_2, cerebral tissue oxygen saturation; RBC, red blood cell; PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage. [a] Mechanical ventilation indicates synchronized intermittent positive pressure ventilation, synchronized intermittent mechanical ventilation, or high-frequency oscillation. [b] Treatment with dopamine and/or dobutamine. [c] PDA indicates a hemodynamically significant left-to-right shunt that required treatment according to the team of neonatologists and cardiologists, that is, a symptomatic PDA.

Table 2. The quality of the general movements and the optimality score

	Median (range) or *n* (%)
Quality of GMs	
Normal GMs	11 (17)
Poor repertoire	47 (72)
Chaotic	0 (0)
Cramped-synchronized	0 (0)
Motor optimality score	
GMOS	27 (18–42)
Not assessable	
Hypokinetic	7 (11)

GMs, general movements; GMOS, general movement optimality score.

Table 3. Odds ratios for risk factors in relation to abnormal GMs on day 8 using univariate and multiple regression analyses

	Univariate analysis		Multivariate model 1[a]		Multivariate model 2[b]	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Hb on day 1, mmol/L	0.44 (0.25–0.78)	<0.01*	0.39 (0.18–0.86)	0.02		
Hb on day 1, mmol/L, no transfusions < day 8 (n = 45)	0.50 (0.28–0.91)	0.02	na		na	
Hb on day 8, mmol/L	0.54 (0.35–0.84)	<0.01*	0.85 (0.48–1.51)	0.57		
r_cSO_2 on day 1, per 10%	0.33 (0.10–1.04)	0.06*			0.29 (0.08–1.03)	0.06
Year of birth	0.99 (0.82–1.18)	0.88				
Gestational age, weeks	0.50 (0.27–0.90)	0.02[Δ]				
SNAPPE-II	1.06 (0.98–1.16)	0.16*	1.12 (1.00–1.24)	0.05	1.07 (0.98–1.17)	0.15
Apgar score at 5 min	0.89 (0.58–1.31)	0.50				
SGA	0.40 (0.10–1.69)	0.21				
R^2 value of the multivariate model			0.44		0.17	

GMs, general movements; OR, odds ratio; CI, confidence interval; Hb, hemoglobin; na, not applicable; r_cSO_2, cerebral tissue oxygen saturation; SNAPPE-II, score for neonatal acute physiology-perinatal extension II; SGA, small-for-gestational age (<10th percentile). * $p < 0.2$, included in the multivariate model. [Δ] Not included in multivariate models because of multicollinearity. [a] Included in this model were Hb on day 1, Hb on day 8, and SNAPPE-II. [b] Included in this model were r_cSO_2 and SNAPPE-II.

Table 4. Relation between risk factors and GMOS on day 8 using univariate and multiple regression analyses

	Univariate analysis		Multivariate model 1[a]		Multivariate model 2[b]	
	B (95% CI)	*p* value	B (95% CI)	*p* value	B (95% CI)	*p* value
Hb on day 1, mmol/L	0.91 (0.18–1.65)	0.02*	0.89 (0.13–1.64)	0.02		
Hb on day 1, mmol/L, no transfusions < day 8 (n = 45)	0.29 (−1.02 to 1.61)	0.66	na		na	
Hb on day 8, mmol/L	0.88 (−0.13 to 1.89)	0.09*	0.29 (−0.72 to 1.29)	0.57		
r_cSO_2 on day 1, per 10%	1.49 (−0.88 to 3.86)	0.19*			1.14 (−1.11 to 3.38)	0.31
Year of birth	−0.25 (−0.71 to 0.21)	0.27				
Gestational age, weeks	1.74 (0.76–2.71)	0.01[Δ]				
SNAPPE-II	−0.27 (−0.44 to −0.09)	<0.01*	−0.27 (−0.44 to −0.10)	<0.01	−0.26 (−0.43 to −0.08)	0.01
Apgar score at 5 min	0.21 (−0.88 to 1.30)	0.70				
SGA	0.37 (−3.00 to3.73)	0.83				
R^2 value of the multivariate model			0.25		0.16	

GMOS, general movement optimality score; B, unstandardized coefficient; CI, confidence interval; Hb, hemoglobin; na, not applicable; r_cSO_2, cerebral tissue oxygen saturation; SNAPPE-II, score for neonatal acute physiology-perinatal extension II; SGA, small-for-gestational age (<10th percentile). * $p < 0.2$, included in the multivariate model. [Δ] Not included in multivariate models because of multicollinearity. [a] Included in this model were Hb on day 1, Hb on day 8, and SNAPPE-II. [b] Included in this model were r_cSO_2 and SNAPPE-II.

sessed in 58 (89%) infants. Of these, 11 infants (19%) had normal GMs and 47 (81%) had poor repertoire GMs. The median GMOS was 27 (IQR 23–33).

Relation between Hb, Cerebral Oxygenation, and Quality of GMs

Low Hb on both day 1 and day 8 was associated with a higher risk of abnormal GMs on day 8 (Table 3). Hemoglobin on day 1 correlated strongly with mean r_cSO_2 on day 1 (Fig. 1). Low r_cSO_2 tended to be associated with a higher risk of abnormal GMs (Table 3). Higher GA was associated with lower risk of abnormal GMs. Neither year of birth, Apgar score, SNAPPE-II, nor SGA was significantly related to abnormal GMs.

Because Hb correlated strongly with r_cSO_2, we entered Hb and r_cSO_2 into separate regression models to avoid multicollinearity. After adjusting for illness severity, only Hb on day 1 remained significantly associated with abnormal GMs on day 8, with model 1 explaining 44% of the variance (Table 3). The association remained signifi-

cant when only the 45 infants were analyzed who did not receive an RBC transfusion before day 8. With regard to its association with abnormal GMs, r_cSO_2 just failed to reach significance ($p = 0.06$), with model 2 explaining 17% of the variance.

Relation between Hb, Cerebral Oxygenation, and GMOS

Low Hb on day 1 was associated with lower GMOSs on day 8 (Table 4). The association disappeared when only infants who did not receive a transfusion within the first week were analyzed. r_cSO_2 was not significantly associated with GMOS ($p = 0.19$). Lower GA and higher SNAPPE-II scores were related to lower GMOSs on day 8, while year of birth, Apgar scores, and SGA were not.

In Table 4, we present 2 separate multivariate models to test whether Hb and r_cSO_2 contributed to the GMOSs. After checking the univariate betas, SNAPPE-II scores, and not GA, were entered in the multivariate models. Both Hb on day 1 and illness severity remained associated with GMOS on day 8, with model 1 explaining 25% of the variance, whereas r_cSO_2 did not, with model 2 explaining 16% of the variance.

Discussion

We demonstrated that in preterm infants, low Hb on the first day after birth was associated with impaired neurological functioning on day 8 as measured in terms of the quality of GMs, including the detailed characteristics of these movements. On day 1, cerebral oxygenation, which is strongly related to Hb, tended to be associated with early neurological functioning. Cerebral injury associated with low Hb on day 1 might be mediated through lower r_cSO_2, irrespective of illness severity.

As we hypothesized, low Hb after birth negatively affected the neurological condition of preterm infants on day 8. Early GMs were assessed only 1 week later, which supported the notion of causality between Hb on day 1 and poor neurological functioning on day 8. The infants had no history of other diseases that might also have affected neurological functioning: Hb remained strongly related to neurological functioning after adjusting for illness severity. In part, the association between Hb and GMs may be mediated by low r_cSO_2 on day 1, seeing that r_cSO_2 was strongly correlated to Hb. Low Hb, however, contributed to both abnormal GMs and lower GMOSs more strongly than r_cSO_2. This might be explained by the fact that not only cerebral hypoxia but also cerebral hyperoxia is associated with poorer outcomes [6], reducing the linear, statistically significant relationship between r_cSO_2 and GMA. Hyperoxia and oxidative stress in particular are associated with white matter and neuronal injury [17, 18]. Our results suggest that anemic hypoxia on day 1 may be harmful for the preterm brain. In line with our results, previous reports showed that increasing compensatory cerebral blood flow during anemia seems insufficient to normalize cerebral oxygenation [4].

A further explanation for the association between low Hb and poor neurological functioning may be that anemia is often associated with poorer hemodynamic stability and increased severity of cardiorespiratory illness and poorer short-term outcomes [19]. This is supported by the fact that early illness severity was also associated with GMA on day 8. Seeing that we excluded infants with severe IVH (≥grade III), this could not have confounded our findings. All anemic infants received an RBC transfusion. Transfusions are also associated with poorer neurological outcomes in preterm infants [20]. Early RBC transfusions may, at least partly, account for any cerebral injury that may have developed within the first week after birth. Supposed pathophysiological mechanisms may be either an inflammatory response, ischemia-reperfusion injury, and/or oxidative stress [21].

We demonstrated that Hb on day 8 was not associated with neurological functioning on day 8. This suggested that the most sensitive period for anemia-related cerebral injury is shortly after birth. A previous study also reported that low Hb directly after birth was associated with an increased risk of mortality and short-term morbidity [2]. Furthermore, maternal Hb within the optimal range during pregnancy is beneficial for gross motor development of infants [22] and supports this theory.

We performed GMA at the end of the first week. The quality of GMs and their detailed characteristics is a reliable indicator of neurological functioning in preterm infants from the first week after birth [14]. Although the prognostic value of abnormal GMs during the first week for long-term outcome may be limited, to date, several studies have reported that early abnormal GMs already identify preterm infants at risk of neurological sequelae [23] and cognitive deficits [24]. Further research should reveal whether this is also the case for the association of GMs with Hb.

Our results suggest that cerebral development is hampered by hypoxia following the early anemic state of the preterm infants. It remains unclear, however, at which level of cerebral anemic hypoxia the benefits of RBC

transfusion outweigh its disadvantages. The results of the SafeBoosC II trial did not confirm neurodevelopmental benefits of a reduced burden of cerebral hypoxia [25]. This study, however, was not powered to detect differences in neurodevelopmental impairments and did not restrict determining cerebral hypoxia to the first day, as we did. Previously it had been reported that cerebral hypoxia on day 1 is associated with impaired neurodevelopment [6, 9].

We recognize several limitations of our study. First, the retrospective design may have induced selection bias. The number of video recordings that was unsuitable for our purpose was rather high, considering that 7 infants were categorized as hypokinetic due to sepsis. This may have confounded our results, with sepsis being one of the mechanisms associated with white matter injury. Furthermore, the included sample consisted mainly of preterm born infants >27 weeks of GA. Second, we used data gathered during 3 different periods from 3 different observational studies. This may have resulted in varying clinical practices, although the year of birth was not associated with neurological functioning in our cohort. Furthermore, transfusion guidelines remained similar over the full time period. Third, because low Hb and transfusions are strongly interrelated, we could not entangle their separate effects on early neurological functioning. However, when performing the analyses in only infants who were not treated with a transfusion, the association between low Hb and poor neurological functioning remained. Fourth, infants born after fetal growth restriction were overrepresented in our cohort. Fetal growth restriction, however, did not significantly affect the results on neurological functioning.

Conclusion

This study aimed to investigate the effects of neonatal Hb on the early neurological condition of infants born before 32 weeks of gestation. In this group of preterm infants, low Hb on day 1 was indeed associated with poorer neurological functioning on day 8. The correlation between low Hb and low cerebral oxygenation may reflect an underlying mechanism of cerebral anemic hypoxic injury or dysfunction. Further prospective studies should shed light on the question whether cerebral oxygenation dictates the need for RBC transfusions.

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Statement of Ethics

The study was approved by the Medical Ethics Review Board of the University Medical Center Groningen in accordance with the Helsinki Declaration (METc 2004/232, METc 2012/055, and METc 2013/263). All parents or guardians of the neonates provided their written informed consent regarding the use of clinical data and for making the video recordings.

Conflict of Interest Statement

All authors declare that they have nothing to disclose, financially or otherwise. There are no conflicts of interest.

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Author Contributions

Bos, Kalteren, and Kooi were involved in study concept and design; Kalteren and Mebius were involved in acquisition of data; Kalteren and Mebius were involved in analysis and interpretation of data; Tanis and Verhagen performed prospective studies; Kalteren drafted the manuscript; Bos, Kalteren, Kooi, Mebius, Tanis, and Verhagen critically revised the manuscript for important intellectual content; Bos and Kooi performed study supervision, both current and previous. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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