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Effect of neonatal hemoglobin concentration on long-term outcome of infants affected by fetomaternal hemorrhage

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ABSTRACT

Background: Fetomaternal hemorrhage (FMH) can cause severe morbidity. However, perinatal risk factors for long-term poor outcome due to FMH have not been extensively studied.
Aims: To determine which FMH infants are likely to have neurological sequelae.
Study design: A single-center retrospective observational study. Perinatal factors, including demographic characteristics, Kleihauer–Betke test, blood gas analysis, and neonatal blood hemoglobin concentration ([Hb]), were analyzed in association with long-term outcomes.
Subjects: All 18 neonates referred to a Neonatal Intensive Care Unit of Kagoshima City Hospital and diagnosed with FMH during a 15-year study period. All had a neonatal [Hb] <7.5 g/dL and 15 of 17 neonates tested had Kleihauer–Betke test result >4.0%.
Outcome measures: Poor long-term outcome was defined as any of the following determined at 12 month old or more: cerebral palsy, mental retardation, attention deficit/hyperactivity disorder, and epilepsy.
Results: Nine of the 18 neonates exhibited poor outcomes. Among demographic characteristics and blood variables compared between two groups with poor and favorable outcomes, significant differences were observed in [Hb] (3.6 ± 1.4 vs. 5.4 ± 1.1 g/dL, $P = 0.01$), pH (7.09 ± 0.11 vs. 7.25 ± 0.13, $P = 0.02$) and base deficits (17.5 ± 5.4 vs. 10.4 ± 6.0 mmol/L, $P = 0.02$) in neonatal blood, and a number of infants with [Hb] ≤ 4.5 g/dL (78%[7/9] vs. 22%[2/9], $P = 0.03$), respectively. The base deficit in neonatal arterial blood increased significantly with decreasing neonatal [Hb].
Conclusions: Severe anemia causing severe base deficit is associated with neurological sequelae in FMH infants.

1. Introduction

Fetal blood enters the maternal circulation even during the first trimester [1,2]. A diagnosis of clinical fetomaternal hemorrhage (FMH) is made when fetal blood loss reaches a significant level leading to fetal anemia and clinical symptoms, such as an abnormal fetal heart rate (FHR) patterns and/or fetal hydrops [3–9]. Although FMH of 30 mL or more and 80 mL or more occur in 1 of 333 women [7] and 1 of 1146 women [4], respectively, the majority FMHs of 30 mL or more occur with minimal clinical signs and symptoms in apparently normal pregnancies [7]. Clinically severe FMH with some clinical problems are estimated to occur in 1 of 3000 to 10,000 women [4,6,8,9]. Affected infants may die, survive with disability, or exhibit normal development [4,5,8–11]. FMH was reported to account for approximately 2.0% of infants with cerebral palsy caused by antenatal and/or intrapartum hypoxic conditions [12].

The outcome of infants with FMH may depend on the size of the hemorrhage in relation to the overall fetal blood volume, the rate at which this blood is lost, and whether the event is acute or chronic [5]. However, most of the pertinent literature is in the form of single case reports and small case series [13–19] or focuses on short-term outcomes of FMH infants [8,9]. To our knowledge, there have been only two reports describing long-term outcomes in FMH case series [4,11], perhaps due to the rarity of clinical FMH. These two studies dealt with 12 and 31 FMH infants [4,11].

As the Kagoshima City Hospital Neonatal Intensive Care Unit (NICU) covers an area in which there are approximately 15,000 annual births, we sometimes encounter cases of clinical FMH. This retrospective observational study was performed to determine which FMH infants are likely to have disabilities in relation to perinatal factors.

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2. Methods

This study was conducted after being approved by the institutional review board of Kagoshima City Hospital. The NICU of Kagoshima City Hospital admitted 9833 patients during the 15-year study period from January 1997 through December 2011. Of 9833 patients, 19 infants with a diagnosis of FMH were abstracted from the database of discharge records. After excluding one FMH infant who was diagnosed with trisomy 21, 18 FMH infants were reviewed focusing on the association between perinatal factors and long-term outcomes. The 18 infants were referred to our NICU soon after birth and did not have chromosomal and/or genetic abnormalities or syndromes. The annual number of FMH cases did not change appreciably over the 15-year period (0–3 cases per year).

The following information regarding perinatal factors were obtained from medical charts: FHR tracing, birth weight, gender, Apgar scores at 1 and 5 min, blood pressure and heart rate on admission, hemoglobin concentration ([Hb]) in either the umbilical cord blood or neonatal blood, blood gas analyses and lactate levels in the neonatal blood, and Kleihauer–Betke test results. The neonatal blood samples included those of the vein in three infants, artery in three infants, the capillary blood of the heel in four infants, and undetermined sampling site in eight infants.

The diagnosis of non-reassuring fetal status (NRFS) on antenatal FHR tracing was based on the presence of any of the following: recurrent variable decelerations (VD), recurrent late decelerations (LD), loss of baseline variability (LOV), and sinusoidal heart rate (SHR) pattern [20]. Fetal growth restriction was diagnosed in infants with birth weight less than 10th percentile value of Japanese neonates for each gestational week (GW) at delivery.

All 18 infants were followed up regularly at a 3- to 6-month interval by neonatologists working in our hospital or other institutions with respect to neurological development. The status of neurological development in children who were followed up at other institutions was obtained directly from physicians seeing these children after obtaining permission from parents of these children. The mean duration of follow-up was 32 ± 25 mo (range, 12–112; median, 23 mo). Poor infant outcome was defined as infants with any of following: cerebral palsy (CP), mental retardation (MR), attention deficit/hyperactivity disorder (ADHD), and epilepsy. Other infants without any of the above disabilities were judged as having favorable outcomes in this study.

Statistical analyses were performed using the JMP11© statistical software package (SAS, Cary, NC). Differences between the means were tested by Wilcoxon's rank sum test and categorical variables were compared using Fisher's exact probability test. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

3. Results

All 18 infants had neonatal [Hb] of <7.5 g/dL (Table 1). Kleihauer–Betke test (K–B test) was performed in 17 mothers for anemia in the neonates: test result (fraction [%] of fetal red blood cells present in the maternal circulation) was more than 4.0% in 15 of the 17 mothers tested. A medical chart of Case 14 indicated "positive K–B test result" with missing an actual datum. In Case 9 without K–B test, the diagnosis of FMH was made because no other causative factors for severe anemia such as placenta previa, congenital infection, and blood malignancy were found. Decreased fetal movement (DFM) was present in four mothers (Cases 6, 13, 16, and 17). NRFS on FHR tracing occurred in 17 of the 18 patients. The SHR pattern was seen in two patients (Cases 5 and 16). Physical finding of "pale" was documented in medical charts of 8 infants (Cases 2, 7, 9–11, 15–17). Nine infants exhibited poor outcomes (Table 1), including four infants with CP alone and five infants with each one of following: MR alone, both CP and MR, both CP and ADHD, both CP and epilepsy, and all of CP, MR, and epilepsy. The remaining 9 infants had none of these disabilities and were considered as having favorable outcome (Table 1). Only one infant (Case 9) with a normal FHR tracing was flaccid at birth showing neonatal blood [Hb] of 5.7 g/dL with pH of 7.12, but responded well to resuscitative measures and did not develop neurological disabilities.

Data of the umbilical cord blood [Hb] was available in 10 infants, but those of neonatal blood [Hb] were available in all 18 infants (Tables 1 and 2). There was a statistically significant difference in [Hb] of the neonatal blood as well as [Hb] of the umbilical cord blood between two groups with favorable and poor outcomes (Table 2). The fraction of those with ≤median [Hb] level was significantly greater in the poor outcome group than in the favorable outcome group (Table 2, Fig. 1). The neonatal blood pH was significantly lower and the neonatal blood

Table 1
Characteristics of 18 patients with fetomaternal hemorrhage.

Case	Events	FHR tracing	GW/BW	B–K test	Apgar	[Hb, g/dL]	Neonatal blood	Outcome/age
				Indication/result (%)	1/5 min	UCB/neonate	pH/BD (mmol/L)	
Favorable outcome								
1	NRFS	LD	38/2462	Anemia/11.6	6/9	4.6/4.7	NA/NA	F/12 mo
2	NRFS	LD	41/2840	Anemia/9.2	7/7	NA/6.2	7.02/16.4	F/12 mo
3	NRFS	LOV,LD	37/2322	Anemia/8.2	4/6	6.6/5.5	7.27/16.9	F/12 mo
4	NRFS	VD	39/2902	Anemia/5.5	8/8	5.8/7.1	7.34/3.1	F/1 y 6 mo
5	NRFS	SHR	41/3106	Anemia/4.5	3/6	4.4/4.5	7.27/15.9	F/1 y 1 mo
6	DFM, NRFS	LOV,LD	37/2313	Anemia/9.5	4/5	6.6/5.0	7.23/14.1	F/1 y 2 mo
7	NRFS	VD, PB	37/2432	Anemia/7.0	5/8	NA/3.4	7.41/4.9	F/3 y 6 mo
8	NRFS	LD	30/1418	Anemia/1.0	4/8	5.5/6.2	7.39/4.5	F/3 y 8 mo
9	None	RFS	39/2973	NA	0/0	NA/5.7	7.12/7.2	F/2 y 9 mo
Poor outcome								
10	NRFS	LD	37/2249	Anemia/9.4	1/3	NA/1.8	6.94/25.5	CP, MR, epilepsy/3 y 8 mo
11	NRFS	LD	40/3170	Anemia/10.8	6/8	NA/3.9	NA/NA	CP, MR/12 mo
12	NRFS	LD	37/2430	Anemia/7.2	5/7	3.8/3.1	7.24/16.5	MR/1 y 8 mo
13	DFM, NRFS	LD	38/2250	Anemia/8.4	2/2	3.4/3.4	6.98/17.0	CP, ADHD/4 y 2 mo
14	NRFS	LD	40/3076	Anemia/positive	2/6	4.0/2.7	7.09/21.0	CP, epilepsy/9 y 4 mo
15	NRFS	LOV, PB	38/2352	Anemia/8.5	2/7	NA/3.9	7.12/10.9	CP/1 y 9 mo
16	DFM, NRFS	SHR	37/2594	Anemia/8.5	4/6	NA/2.2	7.10/10.9	CP/4 y
17	DFM, NRFS	LD, PB	39/3279	Anemia/7.5	0/0	NA/5.0	7.03/21.2	CP/3 y 8 mo
18	NRFS	LD, PB	30/876	Anemia/4.5	4/8	4.1/6.1	7.22/9.1	CP/2 y

ADHD, attention deficit/hyperactivity disorder; BD, base deficit; B–K test, Kleihauer–Betke test: BW, birth-weight (g); CP, cerebral palsy; DFM, decreased fetal movement; Events, antenatal/intrapartum events; GW, gestational week at delivery; F, favorable; [Hb], hemoglobin concentration; LD, late deceleration; LOV, loss of variability; MR, mental retardation; NA, not assessed; NRFS, non-reassuring fetal status on fetal hear rate (FHR) tracing; PB, prolonged bradycardia; RFS, reassuring fetal status; SHR, sinusoidal heart rate pattern; UCB, umbilical cord blood; and VD, variable deceleration.