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Management of severe fetal anemia by Doppler measurement of middle cerebral artery: are there other benefits than reducing invasive procedures?

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ABSTRACT

Objective: Doppler measurement of peak velocity of systolic blood flow in the middle cerebral artery (PVS-MCA) can safely replace invasive testing in the diagnosis of fetal anemia in Rh-alloimmunized pregnancies and PSV-MCA is now the reference technique. However, no study has evaluated its impact in antenatal care and in survival rate. Our objective was to evaluate the impact of the measurement of PVS-MCA in antenatal management and neonatal outcome in maternal red cell alloimmunization requiring in utero transfusion (IUT).

Study design: Retrospective study between January 1999 and January 2013. We excluded all cases of hydrops without follow-up before first IUT. From 1999 to 2006, an IUT was indicated on the optical index at 450 nm (Period 1) and was then replaced by the use of PVS-MCA (Period 2).

Results: 77 patients were included, 39 in Period 1 (104 IUT) and 38 in Period 2 (89 IUT). 5 cases of hydrops fetalis (12.8%) were diagnosed during the follow up in Period 1 and none during Period 2. The average number of IUT, the delays between 2 IUT and between last IUET and birth were comparable. The total rate of complication per IUT during the first period was 9.6% vs 1.1% during the second one ($p = 0.01$). The overall survival rate in our population was 34/39 (86.8%) during Period 1 vs 38/38 (100%) during Period 2.

Conclusion: PSV-ACM allowed an improved monitoring with fewer occurrences of hydrops. Conversely, it did not modify antenatal management and timing of delivery.

Introduction

Historical test to evaluate the need for fetal transfusion was serial amniocentesis for the determination of bilirubin levels in amniotic fluid which was then expressed as the change in optical density plotted on a chart devised by Liley [1]. In 2000, Mari et al. developed an non invasive technique with the use of Doppler measurement of peak velocity of systolic blood flow in the middle cerebral artery (PVS-MCA) [2].

Many studies accessed that Doppler measurement of PVS-MCA can safely replace invasive testing in the diagnosis of fetal anemia in Rh-alloimmunized pregnancies and PSV-MCA is now the reference technique [3–9]. It is also used to time serial intra uterine transfusions (IUT) and to decide time of delivery [10–14]. However, no study has evaluated its impact in antenatal care (complication rate, delay between two IUT and between last IUT and birth, etc.) and in survival rate.

Therefore, our aim was to evaluate the impact of PVS-MCA in antenatal management and neonatal outcome in maternal red cell alloimmunization requiring in utero transfusion.

Materials and methods

Study design

This was a retrospective study of all patients followed or referred to our center for fetal anemia due to red-cell alloimmunization and requiring in utero transfusion from January 1999 till

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January 2013. We excluded all cases of hydrops without follow-up before IUT. Ethical approval was granted by the French committee of obstetrics and gynecologic research ethics (CEROG OBS 2012-02-04).

Data concerning the obstetrical histories for each pregnancy and neonatal outcomes were collected. We noted gestational age at first IUT, interval between transfusions and between the last transfusion and delivery. We notified complications after procedure as emergency cesarean section for fetal distress within 24 h after the procedure, rupture of membranes within 7 days after transfusion, chorioamniotis, fetal death and neonatal death. Neonatal outcomes were evaluated: gestational age at birth, birth weight, hemoglobin at birth, neonatal transfer and neonatal care for allo immunization (transfusion, exsanguino transfusion, phototherapy, etc.). The overall survival rate was based on the number of live infants discharged from our neonatal unit. If more than one complication occurred after the same procedure and if it was obvious that the first one induced the following, all were considered as only one complication in the final analysis.

Indication of IUT regarding to fetal anemia diagnosis method

Amniotic-fluid ΔOD450 measurement (January 1999–March 2006): Period 1

An IUT was indicated whenever the optical index at 450 nm (DOD450) result raised the zone III of Liley's diagram and/or in case of hydrops fetalis. The second IUT was performed when the fetal hemoglobin level was estimated to be 7.0 g/dL, as suggested by the anticipated decrease of 0.33 g/dL/day [15]. A sonography was performed each 7 to 15 days to ensure the absence of hydrops or other sonographic signs of fetal anemia.

Doppler studies (April 2006–January 2013): Period 2

After a learning curve and a year period of transition (amniocentesis and PVS-MCA were done together but the decision of IUT was based in the results of the amniocentesis), PVS-MCA definitively replaced amniocentesis. IUT was decided when the measurement of middle cerebral artery peak systolic velocity was up to 1.55 multiples of the median. A referring clinician checked the measurement of PVS-MCA before IUT. The second IUT was performed when the fetal hemoglobin level was estimated to be 7.0 g/dL, as suggested by the anticipated decrease of 0.33 g/dL/day and/or by the assessment of an elevation of the middle cerebral artery peak systolic velocity (up to 1.55 multiples of the median).

During the two periods, IUT was also indicated in case of sonographic sign (as hydrops).

IUT technique and antenatal management

In utero exchange transfusion was performed in our team as described in a previous study [16]. IUT was done till the 34th week of gestation. Beyond this age, the fetal extraction was discussed with the perinatal specialists. During the second period (since 2008), we do delayed umbilical cord clamping at birth in case of suspected severe fetal anemia. During the first period, 4 experimented operators realized the IUT and 6 during the second period (2 of the first period and 4 new).

Statistics

Two groups were defined as described previously. The qualitative variables are expressed as frequency and percentage; quantitative variables are expressed as mean ± standard deviation. Maternal characteristics, IUT and neonatal data were compared between the two periods (see Methods section) using Chi-square test (or Fisher Exact test when expected cell frequencies < 5) for qualitative variable or using Mann–Whitney U test for quantitative variables. A p value less than 0.05 was considered significant. We used the SAS software for analysis (SAS Institute Inc., Cary, NC 25513).

Results

83 patients were referred or followed in our center, 42 during the first period and 41 during the second one. 6 (7.2%) patients were addressed after diagnosis of hydrops, 3 (7.1%) during Period 1 and 3 (7.3%) during Period 2. After exclusion of those cases, 77 patients were finally included in our study (39 in Period 1 and 38 in Period 2).

Table 1 shows characteristics of the population. Age, gestity and type of red-cell alloimmunization were comparable. 62 amniocentesis were performed in 31 patients during Period 1 (82%) with a mean of 1.9 ± 1.1 per pregnancy and none during the second period. In the other 8 patients, IUT was indicated on sonographic signs (hydrops or effusion). 5 cases of hydrops fetalis (12.8%) were diagnosed during the follow up during Period 1. Hydrops appeared between two sonographies in 2 cases, and after reassuring (Liley I or IIA) amniocentesis in 3 cases. No cases of hydrops occurred in the second group.

104 IUT were performed during the first period and 89 during the second one. Characteristics of IUT are shown in Table 2. The average number of IUT/patient was not significantly different between the two groups (2.7 ± 1.4 vs 2.3 ± 1.1, $p = 0.38$).

Table 1
Maternal characteristics.

	Period 1 ($n = 39$)	Period 2 ($n = 38$)	p.
Age (years)	30.3 ± 5.3	32.7 ± 5.8	0.06
Gestity	3.1 ± 1.6	3.0 ± 1.8	0.7
Maternal antibodies			
Principal antibody			0.73
RH1	31 (82)	30 (78.9)	–
RH 3 (Anti-E)	3 (7.7)	0.0 (0.0)	–
RH 4 (Anti-c)	1 (2.6)	3 (7.9)	0.48
Kell	3 (7.7)	5 (13.2)	0.21
Presence of 2 Antibodies	24 (64.1)	19 (50)	0.18
Presence of 3 Antibodies	10 (25.6)	5 (13.5)	
Amniocentesis	31 (82)	0 (0.0)	<.0001
No. of amniocentesis	1.9 ± 1.1	–	–

Results expressed as mean ± standard deviation or n (%).

Table 2
Intra uterine exsanguino transfusion (IUET).

	Period 1	Period 2	p
Data per patient	($n = 39$)	($n = 38$)	
No. of IUT per patient	2.7 ± 1.4	2.3 ± 1.1	0.38
GA at first IUET (GA)	25.1 ± 3.9	27.7 ± 4.1	0.001
Blood characteristics at 1st IUT			
Hemoglobin	6.4 ± 2.6	6.5 ± 2.7	0.78
Hematocrit	18.5 ± 7.4	20.6 ± 8.1	0.28
Delay between IUT 1 and IUT 2 (d)	18.8 ± 6.4	19.0 ± 9.3	0.95
Delay between last IUT and birth (d)	23.0 ± 11.4	24.8 ± 11.2	0.48
Data per IUT	($n = 104$)	($n = 89$)	
Blood characteristics at IUT			
Hemoglobin	7.0 ± 2.2	7.2 ± 2.4	0.67
Hematocrit	21.6 ± 7.3	21.7 ± 7.4	0.93
Delay between 2 IUT (d)	19.2 ± 5.5	19.3 ± 8.5	0.96
At least one complication	10 (9.6)	1 (1.1)	0.01
Emergency C Section	5 (4.8)	1 (1.1)	–
PROM	2 (1.9)	0	–
Chorioamniotis	0	0	–
Fetal death	4 (3.8)	0	–
Neonatal death	1 (1.0)	0	–

Results expressed as mean ± standard deviation or n (%).
GA: gestational age; IUT: in utero transfusion; PROM: premature rupture of membranes.