Chapter 3

Neonatal outcome in allo-immune thrombocytopenia after maternal treatment with antenatal intravenous immunoglobulin

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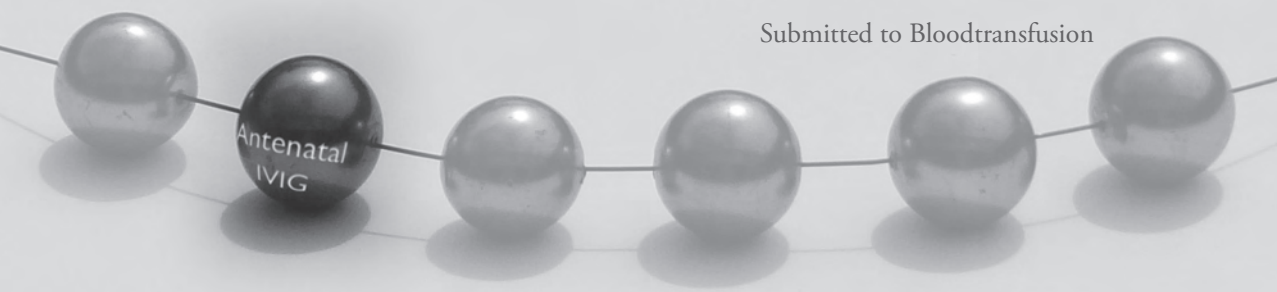

Abstract

Background and objectives

Weekly maternal intravenous immunoglobulin (IVIG) is the cornerstone in antenatal treatment of fetal and neonatal allo-immune thrombocytopenia (FNAIT). The aim of this study was to describe the neonatal outcome and management in neonates with FNAIT treated antenatally with IVIG.

Materials and methods

All neonates treated antenatally and delivered at our center between 2006 and 2012 were included in the study. We assessed the neonatal outcome and management, including the occurrence of intracranial hemorrhage (ICH), platelet count at birth and need for postnatal platelet transfusions or postnatal IVIG treatment.

Results

A total of 23 neonates were included of which 12 (52%) had severe thrombocytopenia at birth (platelet count $\leq 50 \times 10^9$/L). Most neonates (75%, 9/12) with severe thrombocytopenia received a platelet transfusion after birth. None of the neonates required postnatal treatment with IVIG. Three neonates had petechiae and hematomas, without clinical consequences. One neonate suffered from ICH, which was detected just before the planned start of antenatal IVIG at 28 weeks' gestation.

Discussion

Our results suggest that antenatal maternal IVIG and, if necessary, postnatal matched platelet transfusions, are effective and safe for treatment of FNAIT.

Introduction

Fetal and neonatal allo-immune thrombocytopenia (FNAIT) is the most common cause of isolated severe thrombocytopenia in the fetus and neonate.[1-3] It is caused by maternal allo-antibodies against antigens of paternal origin on fetal platelets, resulting in platelet destruction and severe fetal and neonatal thrombocytopenia.[4] In 80-95% of the affected cases, FNAIT is caused by fetomaternal incompatibility for human platelet antigen 1a (HPA 1a).[5-8] Approximately 2% of the Caucasian women are HPA-1a-negative (HPA-1bb), of which only 8-12% will become immunized and produce allo-antibodies.[9-14] The most feared complication of severe neonatal thrombocytopenia is intracranial hemorrhage (ICH), with an incidence of 14-20% in untreated first pregnancies affected with FNAIT.[5,15-17] The majority of ICH occurs at the end of the second trimester and clinical outcome are devastating for most cases.[18,19]

The main treatment goal in FNAIT is prevention of (intrauterine) ICH. The optimal antenatal management is controversial and includes an invasive strategy with repeated fetal blood sampling and intrauterine platelet transfusions (IUPT) or a non-invasive strategy with weekly maternal antenatal IVIG.[6,20] Our center, the Leiden University Medical Center (LUMC), is the national referral center for FNAIT-cases in the Netherlands. Our management changed over time from an invasive to a non-invasive strategy.[6] Although antenatal IVIG administration has become the cornerstone of current treatment, questions remain about the optimal dose, best gestational age to start and the exact mechanisms of action.[21] In addition, little is known about the optimal postnatal management. Treatment of first choice after birth is transfusion of matched platelets, but in case of emergency without immediate availability, random platelets are also given. Postnatal IVIG is effective in increasing platelet counts, but the response is much slower compared to platelet transfusions and the risk of destruction of transfused random platelets exists.[15,16,22-24] The aim of this study was to evaluate the neonatal outcome and management in all FNAIT-cases treated antenatally with IVIG during a 6-year period.

Materials and methods

Study population

All infants with FNAIT, treated with antenatal maternal IVIG (Nanogam®) at our center between January 2006 and January 2012, were included in this study. All

these cases were already known due to a previously affected pregnancy and were treated according to a completely non-invasive protocol.[6] Pregnancies were divided in standard and high risk groups, based on the presence or absence of a previous sibling with ICH. In the standard risk group (no sibling with ICH), antenatal IVIG was started at a gestational age of 28 weeks. In the high risk group (previous sibling with ICH), IVIG treatment was started earlier, at 16-18 weeks' gestation. Between 2005 and 2008 the LUMC participated in the NOICH-trial, in which mothers were randomized for a dosage of 0.5 or 1 g/kg maternal weight. The trial was prematurely stopped in 2008 due to shortage of inclusions, however all FNAIT cases are still prospectively collected in an international web-based registry (www.medscinet.com/noich/).
Since 2008, dosage of IVIG in patients with standard risk pregnancies varies between 0.5 g/kg and 1 g/kg maternal weight. Dosage of IVIG in high risk pregnancies is 1 g/kg maternal weight.
At birth, platelets were determined from the umbilical cord using a standardized flow cytometric method, in case of thrombocytopenia <100 x 10^9/L, platelet count determination was repeated manually. Neonates were examined to rule out the presence of hematomas and petechiae. A cranial ultrasound examination was performed in all neonates within 24 hours postpartum. Matched platelet transfusions were administered if platelet count was ≤ 50 x 10^9/L in bleeding neonates or < 30 x 10^9/L in non-bleeding neonates. In 2010, the transfusion trigger for non-bleeding neonates was lowered to 20 x 10^9/L. HPA-1bb/5aa-typed platelet concentrates were available 24 hours a day. In case of emergency (i.e. clinical bleeding) and no immediate availability of matched platelets, random platelets were transfused. When multiple matched platelet transfusions did not result in sufficient rise of platelet count, treatment with IVIG was considered. No strict criterion for the start of IVIG was maintained. Platelet counts were determined at least daily during the first days of life, until a spontaneous rise or stable level was observed. The postnatal protocol was independent of inclusion in the NOICH-study.

Data collection

Data were collected retrospectively and entered in a database, which included also data about previous pregnancies. Antenatal and postnatal baseline characteristics were collected and included HPA incompatibility type, dosage of IVIG, gestational age at start of IVIG, ICH in previous pregnancy, mode of delivery, gestational age at birth, birth weight and Apgar score ≤7 at 5 minutes. Outcome measures were platelet count at birth, presence of hematomas and/or petechiae, occurrence of ICH, number of needed postnatal platelet transfusions

(matched or random), postnatal use of IVIG, course of platelet counts over time and neonatal outcome.

Results

During the 6-year study period, 23 neonates with FNAIT treated with antenatal IVIG were included. Two pregnancies (9%) were considered high risk due to a sibling with ICH, IVIG dosage was set at 1 g/kg starting at 16 weeks' gestation. Twenty-one (91%) pregnancies were considered as standard risk, of which 20 were treated from 28 weeks' gestation onward with 0.5 g/kg or 1 g/kg. Eight pregnancies were included in the NOICH trial and were randomized to receive either 1 g/kg (n=2) or 0.5 g/kg (n=6). One standard risk pregnancy was treated with 1 g/kg maternal weight antenatal IVIG at 35 weeks' gestation, because of a delayed retrospective diagnosis of FNAIT in the previous pregnancy. Another pregnancy in the standard risk population started with 1 g/kg IVIG at 28 weeks' gestation, because of a detected antenatal ICH. No adverse effects of maternal IVIG therapy were reported. A flowchart of all included patients can be seen in figure 1. Baseline characteristics of the included patients are depicted in table 1.

Table 1. Baseline characteristics of included patients (n=23).

		N = 23
HPA type	1a, n (%)	19 (83)
	5b, n (%)	2 (9)
	15a, n (%)	1 (4)
	1a and 5b, n (%)	1 (4)
ICH in previous pregnancy, n (%)		2 (9)
Gestational age at start of IVIG	16 weeks, n (%)	2 (9)
	28 weeks, n (%)	20 (87)
	35 weeks, n (%)	1 (4)
Dosage IVIG	0.5 g/kg, n (%)	17 (74)
	1 g/kg, n (%)	6 (26)
Caesarean delivery, n (%)		8 (35)
Neonates of mothers with miscarriages/spontaneous abortions, n (%)[b]		3 (13)
Gravidity		2.5 ± 1.1 (2-6)
Gestational age at birth, weeks [a]		37.3 ± 1.6 (33-39)
Birth weight, gram [a]		2922 ± 526 (1855-3730)
Apgar score <7 at 5 minutes, n (%)		0 (0)

[a] Value given as mean ± SD (range)
[b] Two included neonates were siblings, so in total two mothers in the population had miscarriages or spontaneous abortions.

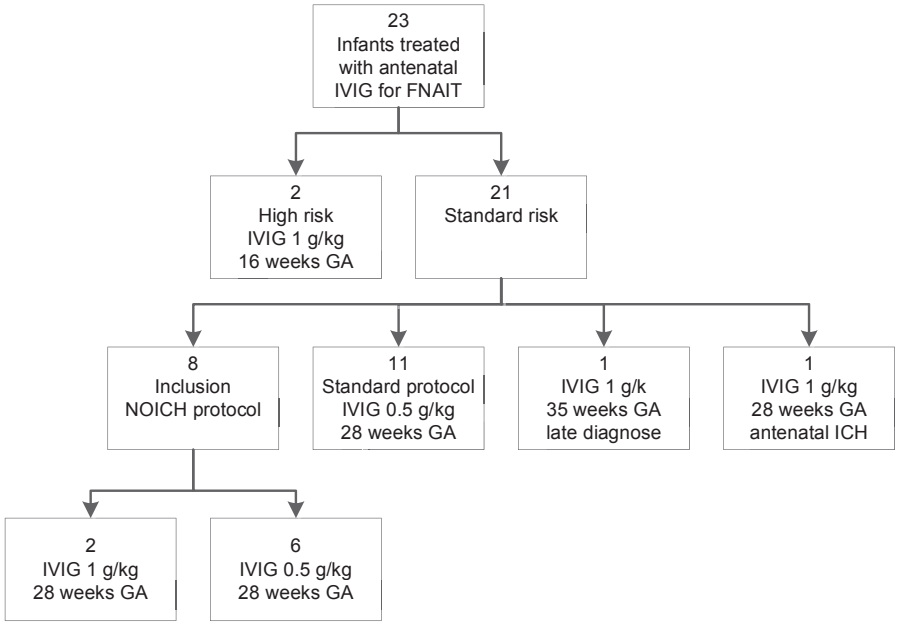

Figure 1. Flowchart of included patients.

Abbreviation:
GA: Gestational age.

Mean platelet count at birth was 91 ± 88 x 10^9/L (range: 6-277 x 10^9/L) and severe thrombocytopenia (platelet count ≤ 50 x 10^9/L) was detected in 12 (52%) neonates. Mean platelet count at birth was 104 ± 89 x 10^9/L in neonates which received 0.5 g/kg IVIG antenatally and 55 ± 83 x 10^9/L in those who received 1 g/kg IVIG. In the group with severe thrombocytopenia, eight neonates required 1 matched platelet transfusion and one neonate needed 2 platelet transfusions, whereas in three neonates the platelet count increased spontaneously. None of the neonates received postnatal IVIG. Mean age at the time platelet count achieved a safe level above 150 x 10^9/L was 3.0 ± 1.6 (1-7) days. Five infants were discharged with a stable platelet count between 100 and 150 x 10^9/L. Individual course of platelet counts of treated neonates is graphically shown in figure 2.

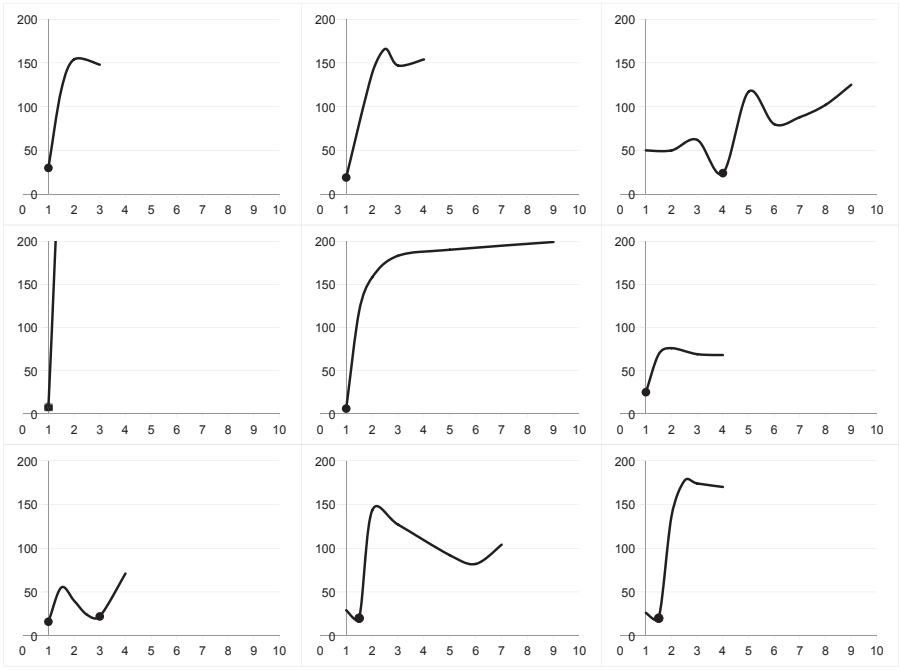

Figure 2. Individual course of platelet count per day.

Legend: Dots indicate the time of platelet transfusions.

Routine cranial ultrasound was performed in all neonates. One neonate had an ICH, which was detected by coincidence during a routine fetal ultrasound at 27 weeks' gestation, just 1 day before the planned start of IVIG treatment. Platelet count at birth was 6 x 10^9/L and the neonate had several petechiae and hematomas. One matched platelet transfusion was administered at birth with good increment. On the second day of life a MRI of the brain showed a left occipital porencephalic cyst, remnant of the antenatal ICH (figure 3). At 2 years of age, a physical and neurodevelopment assessment (using the Bayley Scales of Infant Development III)[25] was performed showing a normal growth and neurodevelopment outcome. Petechiae were detected in two other neonates with platelets of 29 x 10^9/L and 26 x 10^9/L at birth, both had a good response with 1 matched platelet transfusion.

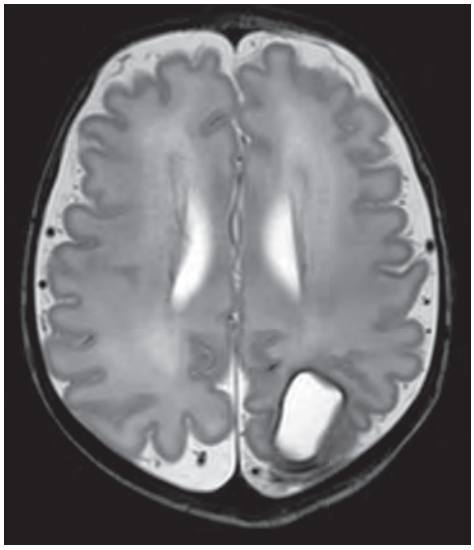

Figure 3. Neonatal cerebral MRI showing a large porencephalic cyst in the left occipital lobe. The cyst is a remnant of a large antenatal ICH, detected at 27 weeks' of gestation.

Five neonates with severe thrombocytopenia were born after 2010, when platelet transfusion trigger in non-bleeding neonates was lowered from 30 x 10^9/L to 20 x 10^9/L platelets. One of them (with a platelet count of 22 x 10^9/L without clinical bleeding) had a spontaneous rise and did not receive a platelet transfusion according to the new protocol. The other 4 infants had platelets <20 x 10^9/L (2) or petechiae or hematomas (n=2) as indication for a platelet transfusion. Table 2 provides an overview of the neonatal outcome.

Table 2. Neonatal outcome.

	N = 23
Platelet count at birth, x 10^9/L[a]	91.1 ± 88.1 (6-277)
Platelet count ≤ 150 x 10^9/L, n (%)	16 (70)
Platelet count ≤ 50 x 10^9/L, n (%)	12 (52)
Platelet count ≤ 30 x 10^9/L, n (%)	9 (39)
Lowest platelet count, days [a]	1.5 ± 0.9 (1-4)
Petechiae and/or hematomas, n (%)	3 (13)
ICH, n (%)	1 (4)
Neonates receiving postnatal platelet transfusions, n (%)	9 (39)
Postnatal age when receiving platelet transfusions, days [a]	1.2 ± 0.7 (1-3)
Postnatal age PC > 150x109/L, days [a]	3.0 ± 1.6 (1-7)

[a] Value given as mean ± SD (range)

Discussion

This cohort study shows a favorable neonatal outcome in FNAIT after non-invasive antenatal maternal treatment with IVIG. Approximately one third (8/23) of the neonates required matched platelet transfusions at birth with a rise in platelets within a few hours and postnatal IVIG was not necessary. An antenatal ICH was detected in only 1 infant at 27 weeks of gestation, just before the start of antenatal IVIG. Despite the cerebral injury, the infant showed a normal neurobehavioral outcome at 2 years of age. Non-invasive management of FNAIT with antenatal maternal IVIG and postnatal matched platelet transfusions seems to be effective and safe.

In this study, approximately one half (12/23) of the neonates had a platelet count at birth ≤ 50 x 10^9/L. The incidence of severe thrombocytopenia found in this study is similar to the incidence reported in several other cohorts (range 34% to 61%).[16,26,27] Berkowitz et al reported a lower incidence of severe thrombocytopenia (14%), but they included only infants without siblings with severe thrombocytopenia or ICH.[28] A sibling with ICH or severe thrombocytopenia is one of the most important risk factors for recurrence of severe thrombocytopenia.[29] Besides neonates with HPA1a-incompatability, we also included cases with HPA5b-incompatibility (2) and HPA15a-incompatibility (1). The incidence of severe thrombocytopenia reported in this study may be influenced by the fact that HPA5b incompatibility is associated with less severe thrombocytopenia.[18,30]

The incidence of ICH in our study was 4% (1/23) and concurrent with the incidence reported by others (range 0-10%).[5-7,16,26-28,31] The only infant with ICH in our study did not have a sibling with ICH and was therefore planned to start with IVIG at 28 weeks of gestation (standard risk group). However an ICH was detected just 1 day before starting IVIG. Whether starting IVIG before 28 weeks of gestation could have prevented of the development of ICH is not known. Consensus on the optimal timing of starting the treatment with IVIG is currently lacking. In our study, severe thrombocytopenia at birth was not associated with an increased rate of ICH. As previously suggested, our study confirms the possible protecting effect of IVIG for ICH even without an increase in fetal platelet counts.[27,32,33] In addition, all infants had an adequate and quick response on postnatal matched platelet transfusions and postnatal IVIG was not necessary. This positive effect of antenatal IVIG in combination with postnatal matched platelet transfusions was also reported in earlier studies.[16,22,24] In contrast to our observations in human beings, reduction of bleeding complications in mouse studies with IVIG was accompanied by an increase of platelet counts.[34]

Several questions on the optimal IVIG treatment remain unanswered, including the optimal dose (0.5 or 1 g/kg), schedule (weekly or more frequently) and gestational age to initiate antenatal IVIG. Our study was not designed nor powered to analyze these issues and was primarily focused on postnatal management. Currently, a large international web-based registry of all FNAIT cases (prospective continuation after the NOICH-trial) may shed more light on this subject in the near future. Data on timing of antenatal intracranial hemorrhages with suggestions for gestational age to initiate antenatal IVIG have already been published.[19]

Prevention of ICH in unknown first cases of FNAIT may also be achieved using antenatal screening on HPA1a negative genotypes in all pregnant women. Still more studies suggest the level of maternal antibody titer during pregnancy as a possible predicting factor for severe thrombocytopenia, although the diagnostic value is not clear as reliable cut off levels were not repeatedly demonstrated yet.[9,13,16] Kjeldsen et al suggested a policy of antenatal screening for immunized HPA1a negative pregnant women and performing a cesarean section at a gestational age of 36-38 weeks. Their incidence of ICH was 2 out of 170 immunized HPA1a negative women, although with lacking control group with at term vaginal delivery no strict conclusions can be drawn from this study.[35] More research is needed to identify women at greatest risk in order to investigate the advantages of offering antenatal treatment with maternal IVIG in a more targeted way.

The retrospective design of this study is a limiting factor; we tried to minimize possible

bias by using strict definitions and cut off values. Another limitation is the relatively small sample size, due to the rarity of this disease. However, sufficient retrospective evidence is needed to design and perform ethical justified randomized controlled trials. In conclusion, our study results suggest that non-invasive antenatal treatment of FNAIT with weekly maternal IVIG and, if necessary, postnatal transfusion of matched platelets is safe and effective. We recommend the use of matched platelets to non-bleeding neonates with a platelet count of < 20 x 10^9/L and to bleeding neonates with a platelet count < 50 x 10^9/L. In general, postnatal IVIG administration can be omitted. More research is needed to optimize dose and schedule of antenatal IVIG treatment and to detect more predicting factors of severe fetal or neonatal thrombocytopenia.

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