Postnatal treatment for children with fetal and neonatal alloimmune thrombocytopenia: a multicentre, retrospective, cohort study

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Summary

Background Children affected by fetal and neonatal alloimmune thrombocytopenia (FNAIT) are at risk of severe intracranial haemorrhage. Management in the postnatal period is based on sparse evidence. We aimed to describe the contemporary management and outcomes of patients with FNAIT in high-income countries.

Methods In this multicentre, retrospective, cohort study, we set up a web-based registry for the collection of deidentified data on the management and course of neonates with FNAIT. Eight centres from seven countries (Australia, Norway, Slovenia, Spain, Sweden, the Netherlands, and the USA) participated. Eligibility criteria comprised neonates with FNAIT being liveborn between Jan 1, 2010, and Jan 1, 2020; anti-human platelet antigen (HPA) alloantibodies in maternal serum; confirmed maternal and fetal HPA incompatibility; and bleeding detected at antenatal ultrasound, neonatal thrombocytopenia (<150×10^9 platelets per L), or both in the current or previous pregnancy. Clinical data were retrieved from local medical records of the first neonatal admission and entered in the registry. The key outcome was the type of postnatal treatment given to neonates with FNAIT. Other outcomes were daily median platelet counts in the first week of life, median platelet count increment after first unmatched versus first matched transfusions, and the proportion of neonates with mild or severe bleeding.

Findings 408 liveborn neonates with FNAIT were entered into the FNAIT registry, of whom 389 from Australia (n=74), Norway (n=56), Slovenia (n=19), Spain (n=55), Sweden (n=31), the Netherlands (n=138), and the USA (n=16) were included in our analyses. The median follow-up was 5 days (IQR 2–9). More neonates were male (241 [64%] of 379) than female (138 [36%]). Severe thrombocytopenia (platelet count <50×10^9 platelets per L) was reported in 283 (74%) of 380 neonates, and extreme thrombocytopenia (<10×10^9 platelets per L) was reported in 92 (24%) neonates. Postnatal platelet count nadir was higher in the no-treatment group than in all other groups. 163 (42%) of 389 neonates with FNAIT received no postnatal treatment. 207 (53%) neonates received platelet transfusions, which were either HPA-unmatched (88 [43%] of 207), HPA-matched (84 [41%]), or a combination of both (35 [17%]). The proportion of neonates who received HPA-matched platelet transfusions varied between countries, ranging from 0% (Slovenia) to 63% (35 of 56 neonates; Norway). Postnatal intravenous immunoglobulin treatment was given to 110 (28%) of 389 neonates (alone [n=19] or in combination with platelet transfusions [n=91]), with the proportion receiving it ranging from 12% (17 of 138 neonates; the Netherlands) to 63% (ten of 16 neonates; the USA) across countries. The median platelet increment was 59×10^9 platelets per L (IQR 35–94) after HPA-unmatched platelet transfusions and 98×10^9 platelets per L (67–134) after HPA-matched platelet transfusions (p<0·0001). Severe bleeding was diagnosed in 23 (6%) of 389 liveborn neonates, with one having a severe pulmonary haemorrhage and 22 having severe intracranial haemorrhages. Mild bleeding was diagnosed in 186 (48%) neonates.

Interpretation Postnatal management of FNAIT varies greatly between international centres, highlighting the absence of consensus on optimal treatments. Our data suggest that HPA-matched transfusions lead to a larger median platelet count increment than HPA-unmatched transfusions, but whether HPA matching is also associated with a reduced risk of bleeding remains unknown.

Funding Sanquin.

Introduction

Children affected by fetal and neonatal alloimmune thrombocytopenia (FNAIT) have an increased risk of bleeding during pregnancy and after birth. Incompatibility in human platelet antigens (HPAs) between mother and fetus can lead to a maternal alloimmune response, with the formation of anti-HPA alloantibodies. Platelet-directed antibodies (IgG) are

Research in context

Evidence before this study

We searched PubMed without language restrictions for studies published between database inception and April 27, 2022, reporting on postnatal treatment and outcomes in patients with fetal and neonatal alloimmune thrombocytopenia (FNAIT). Search terms related to the postnatal management and outcomes of patients with FNAIT were used. We identified four prospective and ten retrospective cohort studies. Available studies had methodological limitations, including small numbers of patients, no randomisation, and no analyses of confounding factors. Optimal postnatal management of FNAIT is not known; guidelines are based on sparse qualitative evidence owing to the rarity of the condition. None of the studies we found compared postnatal management strategies between different countries. The standard of care and whether postnatal management varies between international referral centres is unknown.

Added value of this study

To our knowledge, this multicentre study is the first to investigate postnatal treatment strategies and outcomes of neonates affected by FNAIT in different countries. We gathered data from seven different countries and 389 neonates with FNAIT and found great variation in postnatal management strategies, particularly in the use of human platelet antigen (HPA)-matched platelet transfusions and intravenous immunoglobulins.

Implications of all the available evidence

This study shows variation in postnatal treatment strategies for FNAIT. HPA-matched or HPA-unmatched platelet transfusions and intravenous immunoglobulins are frequently administered postnatally; however, the efficacy of these treatment strategies is unknown. Our findings could motivate international collaboration through multicentre, randomised trials aimed at improving the management and outcomes of patients with FNAIT. Data from this study can serve as a basis from which future clinical trials can be designed.

actively transported across the placenta into the fetal circulation. These alloantibodies bind to platelets and, possibly, endothelial cells, resulting in fetal thrombocytopenia and an increased risk of bleeding.[1–3] FNAIT is the leading cause of severe thrombocytopenia in otherwise healthy full-term neonates and occurs in approximately one in 1500 pregnancies.[4,5]

The main goal of antenatal and postnatal management of FNAIT is to prevent severe fetal and neonatal intracranial bleeding and its long-term sequelae. Administration of intravenous immunoglobulin to the mother during pregnancy is often used as a first-line treatment in mothers during pregnancies subsequent to one where FNAIT was diagnosed.[6] However, quantitative evidence supporting postnatal treatment in FNAIT is sparse and there is no international consensus on neonatal management.[7] Given the rarity of this disease, large, prospective, randomised trials are not available. Guidelines are mostly based on small observational studies and expert opinion.[6] We therefore aimed to evaluate international practices in postnatal treatment and the outcomes of patients with FNAIT.

Methods

Study design and participants

For this retrospective cohort study, on Sept 1, 2020, we set up a multicentre, web-based registry for the collection of deidentified data on the postnatal management and course of liveborn neonates with FNAIT. Eight centres from seven countries with specific interest and expertise in FNAIT agreed to participate: the Australian Neonatal Alloimmune Thrombocytopenia registry (Monash University, Melbourne, VIC, Australia), the Arctic University of Norway (Tromsø, Norway), University Medical Centre Ljubljana (Ljubljana, Slovenia), Blood and Tissue Bank (Barcelona, Spain), Karolinska University Hospital (Stockholm, Sweden), Leiden University Medical Center (Leiden, the Netherlands), Sanquin Diagnostics (Amsterdam, the Netherlands), Levine Children's Hospital (Charlotte, NC, USA), and Boston Children's Hospital (Boston, MA, USA; appendix p 2). Investigators were supplied with personal credentials to enter clinical data into a secured online database (Castor Electronic Data Capture 2019).

Participants were eligible if they were liveborn between Jan 1, 2010, and Jan 1, 2020, their mothers had anti-HPA alloantibodies in their serum, incompatibility between the maternal and fetal HPAs was confirmed,[8] and they (or a previous pregnancy) had bleeding detected at an antenatal ultrasound, neonatal thrombocytopenia ($<150\times10^9$ platelets per L), or both. The medical ethical committee of Leiden-Delft-DenHaag provided a waiver of consent for the initiating country (the Netherlands; G20.074). The requirement for informed consent was waived. International investigators obtained ethical consent or a waiver of consent according to national laws and regulations.

Procedures

Between Sept 1, 2020, and Sept 1, 2021, the following information was retrieved from local medical records of the first neonatal admission to hospital and entered in the online registry: time of diagnosis (antenatal or postnatal), reason for suspecting FNAIT, anti-HPA alloantibody specificity, method of anti-HPA alloantibody detection, gravidity, parity, the presence of maternal thrombocytopenia, antenatal treatment, gestational age

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See **Online** for appendix

at birth, delivery mode, sex of neonate (as determined by the caregiver directly after birth), birthweight (including percentile and small for gestational age), neonatal skin or organ bleeding, neonatal intracranial haemorrhage (including neuroimaging reports), neonatal mortality, lowest platelet count per day (up to nine platelet counts per participant), postnatal treatment per day during the first admission, and bleeding complications after the start of postnatal treatment.

We defined five postnatal treatment groups: no treatment, platelet transfusion from HPA-unmatched donors, platelet transfusion from HPA-matched donors, HPA-unmatched and HPA-matched platelet transfusions, and postnatal intravenous immunoglobulin. Participants who received a HPA-matched platelet transfusion did so from donors who were HPA-typed and selected on the absence of the implicated HPA. Participants who received both a platelet transfusion and postnatal intravenous immunoglobulin treatment or steroids were not analysed separately but included in a treatment group on the basis of the platelet transfusion received. Platelet transfusion thresholds for participants with and without bleeding and the recommended transfusion doses from clinical guidelines for FNAIT postnatal treatment were reported for each centre.

Antenatal diagnosis of FNAIT was defined as the detection of anti-HPA alloantibodies in the mother's serum during the current or previous pregnancy, with confirmed HPA incompatibility between the mother and fetus in the current pregnancy. Postnatal diagnosis was defined as the detection of anti-HPA alloantibodies after birth. Small for gestational age was defined as a birthweight of less than the 10th percentile according to local or national growth charts. Neonates born from pregnancies during which mothers received antenatal treatment (intravenous immunoglobulins, corticosteroids, intrauterine platelet transfusions, or a combination thereof) are called antenatally treated cases.

Bleeding symptoms were divided into mild and severe bleeding. Mild bleeding was defined as any uncomplicated haemorrhage (eg, petechiae, haematomas, or a grade 1–2 intraventricular haemorrhage [the grading system was adapted from Papile et al[9] and Inder et al[10]]). Severe bleeding was classified by a severe intracranial haemorrhage (a grade 3 intraventricular haemorrhage, an intraventricular haemorrhage of any grade in combination with parenchymal involvement, a parenchymal haemorrhage or cerebellar haemorrhage, a subdural haemorrhage causing parenchymal compression, a subarachnoid haemorrhage, or an epidural haemorrhage), severe organ bleeding (life-threatening bleeding associated with shock or requiring volume boluses, red blood cell transfusions, or inotropes), or both. Asymptomatic cases were participants without any bleeding symptoms. In participants with a severe intracranial haemorrhage, we attempted to estimate the timeframe in which the intracranial haemorrhage could have occurred by recording the date of the latest (antenatal) ultrasound without intracranial haemorrhage and the date at which the intracranial haemorrhage was diagnosed.

Outcomes

Our primary aim was to describe current practice in the postnatal treatment of neonates with FNAIT per country. Our key endpoint was postnatal treatment during first admission, described in the five treatment groups. Other aims were to describe neonatal outcomes and platelet count increments. Endpoints were the daily median postnatal platelet counts in the first week of life in neonates with FNAIT per treatment group, the median change (increment) in platelet count after the first platelet transfusion in recipients of unmatched versus matched platelet transfusions, and the proportion of participants with mild or severe bleeding per treatment group.

Statistical analysis

Study sample size was not based on statistical hypothesis testing. To obtain an overview of contemporary treatment and differences in the postnatal treatment of FNAIT between countries, we aimed to recruit at least 200 neonates from at least six centres. Endpoints were analysed in a population of liveborn neonates with FNAIT who had available information on postnatal treatment. Median platelet counts per day are presented by treatment group and additionally stratified by antenatal treatment status.

To calculate the platelet count increment per transfusion type, we subtracted the minimum platelet count on the day before transfusion or the day of transfusion (whichever was least) from the maximum platelet count on the day of transfusion or the day after transfusion (whichever was most). This choice was made because platelet counts exactly before and after transfusion were not available (only the lowest platelet count per day was documented). Participants who received transfusions on the same day or on the day after the first transfusion or had missing platelet counts for the days of interest were not included in these analyses. Only first transfusions were included in these analyses; subsequent transfusions were not included, because their effects could not be determined without taking the previous transfusion into account. We compared median platelet count increments after transfusion using Mann–Whitney *U* tests (an unadjusted analysis). Because data on confounding variables, such as the volume, concentration, and duration of transfusions, were not available, adjusted analyses were not done. Platelet count increments after transfusion were calculated separately for participants who had or had not received antenatal treatment. We did a subgroup analysis of clinical outcomes and treatment by country to assess differences in FNAIT severity.

Statistical analyses were done in Stata (version 16) and SPSS Statistics (version 26.0). Data are presented as the

numbers of participants and percentages or medians and IQRs. The distributions of postnatal treatment strategies are shown as pie charts and platelet counts are shown as dot plots with medians and IQRs. Figures were made with GraphPad Prism (version 9).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

408 liveborn neonates with FNAIT were entered in the FNAIT registry. We excluded 19 neonates (5%) who had missing information on postnatal treatment, leaving 389 (95%) in our analyses (figure 1). 255 (66%) of 389 cases of FNAIT were diagnosed postnatally (table 1). Postnatal suspicion of FNAIT was due to skin bleeding in 127 (33%) of 389 neonates, thrombocytopenia detected as a chance finding in 118 (30%), and severe bleeding in ten (3%). 134 (34%) neonates were diagnosed antenatally, of whom 117 were diagnosed after a diagnosis of FNAIT in the mother's previous pregnancy. FNAIT was diagnosed antenatally in a screening study or because of a family history of FNAIT in 12 (3%) of 389 neonates. For the remaining five (1%) neonates, FNAIT was suspected due to severe antenatal bleeding. The method of detecting anti-HPA antibodies differed between countries (appendix p 3). Antenatal treatment was given in 105 (78%) of 134 pregnancies that were antenatally diagnosed; the maternal administration of intravenous immunoglobulin was started in all 105 pregnancies, intravenous immunoglobulin was combined with steroids in 12, and intravenous immunoglobulin and steroids were combined with intrauterine platelet transfusions in two. There was an over-representation of male neonates and small-for-gestational-age neonates (table 1). Baseline characteristics, particularly the prevalence of antenatal treatment, varied between countries (appendix p 4).

The median follow-up during admission was 5 days (IQR 2–9). 163 (42%) of 389 neonates with FNAIT received no postnatal treatment (table 2). 207 (53%) neonates received platelet transfusions, which were either random donor, HPA-unmatched platelet transfusions (88 [43%] of 207), HPA-matched platelet transfusions (84 [41%]), or a combination of both (35 [17%]). In the no-treatment group, 77 (47%) of 163 mothers were treated antenatally. The median number of postnatal transfusions given in the total population was 1 (IQR 1–2). The proportion of neonates who received HPA-matched platelet transfusions varied between countries, ranging from 0% (Slovenia) to 63% (Norway; figure 1; appendix p 5).

Postnatal intravenous immunoglobulin treatment was given to 110 (28%) of 389 neonates (alone [n=19] or in combination with platelet transfusions [n=91]), with the proportion receiving it ranging from 12% to 63% across countries (appendix p 5). Four (4%) of 93 neonates with dosing information received a dose of 0·5 g/kg of bodyweight per day of postnatal intravenous immunoglobulin treatment, 85 (91%) received 1·0 g/kg per day,

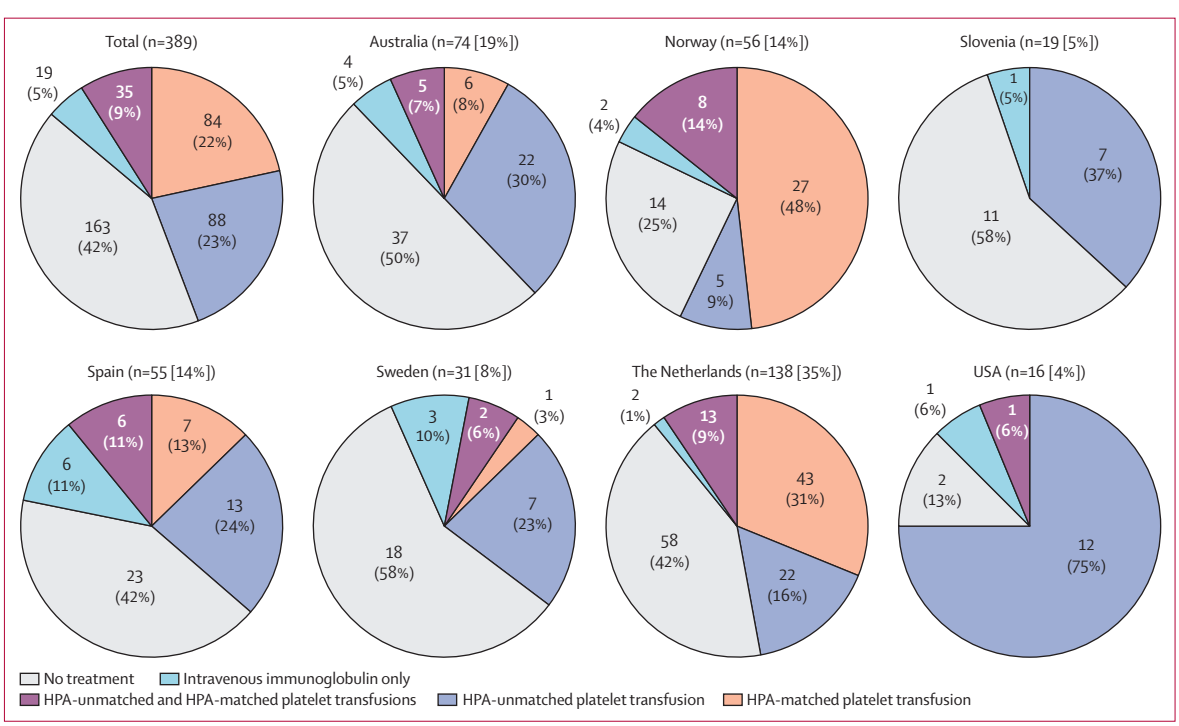

Figure 1: **Postnatal treatment strategies by country**

	Participants (n=389)
HPA specificity	
HPA-1a	291 (75%)
HPA-1b	3 (1%)
HPA-2b	3 (1%)
HPA-3a	3 (1%)
HPA-5a	7 (2%)
HPA-5b	46 (12%)
HPA-15a	3 (1%)
HPA-15b	5 (1%)
HPA-1a and HPA-3a	1 (<1%)
HPA-1a and HPA-5b	8 (2%)
HPA-1b and HPA-5b	2 (1%)
Other	11 (3%)
Unknown	6 (2%)
Antenatal diagnosis*	134 (34%)
Postnatal diagnosis	255 (66%)
Antenatal treatment	105/134 (78%)
First pregnancy (primigravida)†	82 (21%)
Sex	
Female	138/379 (36%)
Male	241/379 (64%)
Gestational age at birth, weeks	38 (37–40)
Birthweight, g	3060 (2584–3441)
Small for gestational age	77/371 (21%)

Data are n (%), n/N (%), or median (IQR). All statistics and percentages were calculated by use of valid numbers, excluding participants with missing data. Ethnicity data are not reported because these data were not routinely noted in medical records. FNAIT=fetal and neonatal alloimmune thrombocytopenia. HPA=human platelet antigen. *117 cases of FNAIT were diagnosed antenatally after a diagnosis of FNAIT in a previous pregnancy. 17 cases of FNAIT were newly diagnosed in the current pregnancy. †82 (30%) of 272 women who had not been previously diagnosed with a FNAIT pregnancy were primigravida.

Table 1: **Clinical characteristics of liveborn neonates with FNAIT**

and four (4%) received 2·0 g/kg per day. The dose of postnatal intravenous immunoglobulin treatment was not known for 17 neonates. Steroid treatment was given to only four neonates from two countries (Spain and the Netherlands). Platelet transfusion guidelines varied between centres, with transfusion thresholds ranging from 20×10^9 platelets per L to 50×10^9 platelets per L in neonates without bleeding and from 50×10^9 platelets per L to 100×10^9 platelets per L in neonates with bleeding (appendix p 6). Transfusion doses varied from 10 mL/kg to 20 mL/kg (appendix p 6).

The median age at detection of platelet count nadir was 0 days (the day of birth; IQR 0–1). In 348 (92%) of 380 neonates with complete data, platelet count nadir was detected at 3 days or earlier. Severe thrombocytopenia was detected in 283 (74%) of 380 and extreme thrombocytopenia was detected in 92 (24%; table 2). Postnatal platelet count nadir was higher in the no-treatment group than in all other groups (table 2). Treatment groups differed in the proportion of neonates who were antenatally treated and in the proportion of neonates who were treated with (additional) postnatal intravenous immunoglobulin (table 2). In all treatment groups, median platelet count increased in the first week after birth (figure 2). The platelet counts of neonates receiving HPA-unmatched platelets were not different from those of neonates receiving HPA-matched platelets after day 3 (figure 2). At day 4, the median platelet count of neonates receiving HPA-unmatched platelets (87×10^9 platelets per L [IQR 48–142]) did not differ from the median platelet count of neonates receiving HPA-matched platelets (125×10^9 platelets per L [70–172]; p=0·15).

50 neonates who did not receive antenatal or postnatal treatment had severe thrombocytopenia (platelet count $<50\times10^9$ platelets per L) and 11 had very severe thrombocytopenia (platelet count $<25\times10^9$ platelets per L); in all 50 neonates, platelet count increased spontaneously within the first week of life (data not shown) and none developed bleeding. Platelet counts during the first week of life stratified by antenatal treatment status are shown in the appendix (p 7). The median nadir platelet count was 110×10^9 platelets per L (IQR 33–191) for neonates who were antenatally treated and 17×10^9 platelets per L (8–20) for neonates who did not receive antenatal treatment. The median nadir platelet counts of neonates were 19×10^9 platelets per L (IQR 9–40) if their mothers had anti-HPA-1a antibodies, 55×10^9 platelets per L (28–146) if their mothers had anti-HPA-5b antibodies, and 39×10^9 platelets per L (16–46) if their mothers had anti-HPA-15b antibodies (the most commonly involved antigens).

207 neonates, of whom 24 (12%) were antenatally treated with intravenous immunoglobulin, received 367 postnatal platelet transfusions. We excluded 81 (39%) neonates from our analysis of post-transfusion platelet count increments, because they either received a second transfusion on the same day as the first transfusion (n=15) or on the day after the first transfusion (n=29) or had missing data (n=37). The platelet increment after the first transfusion was calculated and compared between HPA-unmatched platelet transfusions (n=60) and HPA-matched platelet transfusions (n=66). The median platelet increment was 59×10^9 platelets per L (IQR 35–94) after HPA-unmatched platelet transfusions and 98×10^9 platelets per L (67–134) after HPA-matched platelet transfusions (p<0·0001; figure 3). Our results were similar when stratified by antenatal treatment status (figure 3).

Severe bleeding was diagnosed in 23 (6%) of the 389 liveborn neonates. One neonate had a severe pulmonary haemorrhage; the other 22 neonates were diagnosed with severe intracranial haemorrhages (appendix p 8). Three (14%) cases of intracranial haemorrhage were detected antenatally by ultrasound, 17 (77%) were detected postnatally, and the timepoint of detection was unknown for two (9%). In two of the three neonates who were diagnosed antenatally, antenatal intravenous immunoglobulin treatment was started after

	No postnatal treatment (n=163)	HPA-unmatched platelet transfusion (n=88)	HPA-matched platelet transfusion (n=84)	HPA-unmatched and HPA-matched platelet transfusions (n=35)	Intravenous immunoglobulin only (n=19)	Total (n=389)
Treatment						
Antenatal treatment	77 (47%)	3 (3%)	21 (25%)	0	4 (21%)	105 (27%)
Postnatal treatment						
Intravenous immunoglobulins	NA	42 (48%)	24 (29%)	25 (71%)	19 (100%)	110 (28%)
Additional steroids	NA	1 (1%)	1 (1%)	2 (6%)	NA	4 (1%)
Platelet count*						
Platelet count nadir, $\times 10^9$ platelets per L	65 (34–162)	12 (8–19)	12 (7–18)	6 (3–14)	23 (12–38)	21 (10–51)
Thrombocytopenia (platelet count $<150 \times 10^9$ platelets per L)	111/154 (72%)	88 (100%)	84 (100%)	35 (100%)	19 (100%)	337/380 (89%)
Severe thrombocytopenia (platelet count $<50 \times 10^9$ platelets per L)	58/154 (38%)	88 (100%)	84 (100%)	35 (100%)	18 (95%)	283/380 (74%)
Very severe thrombocytopenia (platelet count $<25 \times 10^9$ platelets per L)	13/154 (8%)†	74 (84%)	75 (89%)	33 (94%)	11 (58%)	206/380 (54%)
Extreme thrombocytopenia (platelet count $<10 \times 10^9$ platelets per L)	1/154 (1%)†	33 (38%)	31 (37%)	23 (66%)	4 (21%)	92/380 (24%)
Severity of bleeding symptoms						
Mild bleeding	39 (24%)	57 (65%)	58 (69%)	24 (69%)	8 (42%)	186 (48%)
Severe bleeding	2 (1%)	10 (11%)	5 (6%)	6 (17%)	0	23 (6%)

Data are n (%) or median (IQR). All statistics and percentages were calculated by use of valid numbers, excluding participants with missing data. FNAIT=fetal and neonatal alloimmune thrombocytopenia. HPA=human platelet antigen. NA=not applicable. *Platelet count data missing for nine patients in the no-treatment group. †The reason why no treatment was given to these thrombocytopenic neonates is unknown. Platelet counts were less than 25×10^9 platelets per L for 1 day in all 14 neonates.

Table 2: **Postnatal treatment and outcomes of liveborn neonates with FNAIT**

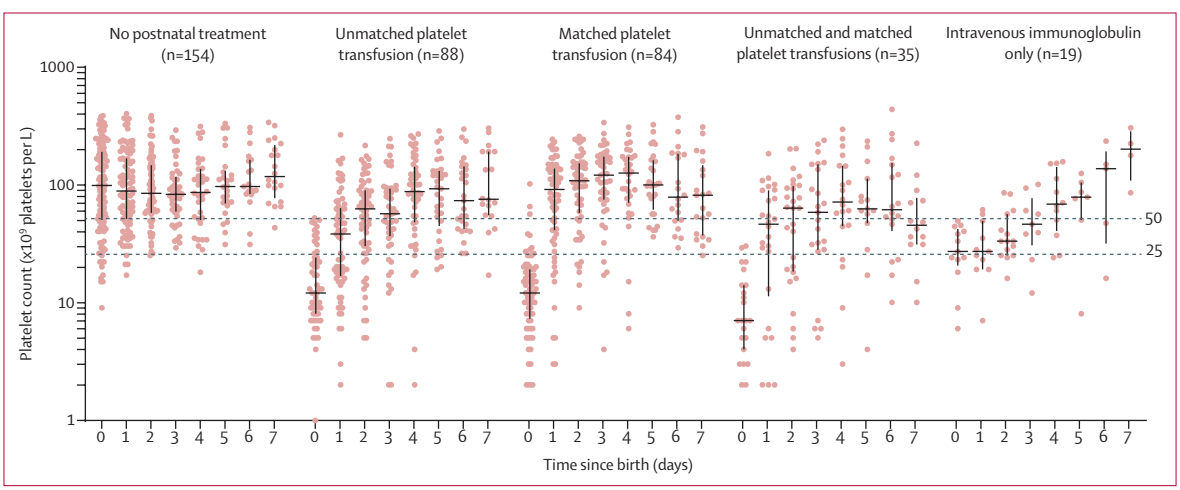

Figure 2: **Platelet counts in the first week of life by postnatal treatment strategy**
The dot plot shows the lowest neonatal platelet count per day per treatment strategy. The dots represent individual platelet counts, the solid, black, horizontal lines represent median values, and the vertical, solid, black lines represent IQRs. Dashed lines represent platelet counts of 50×10^9 platelets per L and 25×10^9 platelets per L.

the detection of anti-HPA antibodies in the mother's serum at 20 weeks' gestational age and 32 weeks' gestational age, respectively. Estimating the timepoint of severe intracranial haemorrhage development was not possible in 16 (73%) of 22 neonates owing to missing data and the lack of serial ultrasound examinations during pregnancy and after delivery. In one neonate with a severe intracranial haemorrhage diagnosed postnatally, the bleeding worsened postnatally on MRI after the initial diagnosis. In this neonate, platelet count nadir was 19×10^9 platelets per L on day 5 after birth and the implicated antibody was directed against HPA-15b. No other worsening of severe bleeding was reported for the other neonates.

Mild bleeding was diagnosed in 186 (48%) of 389 neonates, of whom eight (4%) had a mild intracranial haemorrhage, eight (4%) had mild organ bleeding, and 170 (91%) had skin bleeding. Of the eight neonates who had a mild intracranial haemorrhage, five (63%) had a grade 1 intraventricular haemorrhage and three (38%)

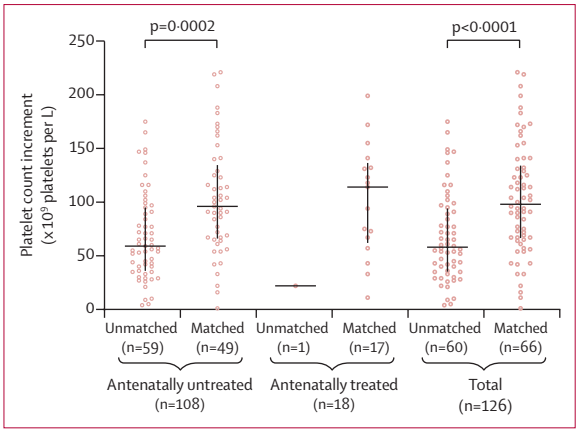

Figure 3: **Platelet count increment after first platelet transfusion**
The dots represent individual platelet increments, the solid, black, horizontal lines represent median values, and the vertical, solid, black lines represent IQRs. Median platelet count increments were compared by use of the Mann–Whitney *U* test (unadjusted analysis). Statistical testing in the antenatally treated group was not possible because only one neonate in this subgroup received an unmatched platelet transfusion.

had an intracranial haemorrhage that was not specified. Five of the eight neonates who had mild organ bleeding had gastrointestinal bleeding, two had umbilical cord bleeding, and one had a retinal haemorrhage. None of the neonates who had a previous sibling diagnosed with FNAIT were diagnosed with intracranial haemorrhage. In our subgroup analysis assessing treatment and clinical outcome by country, differences were observed in the proportion of neonates who were antenatally treated, ranging from three (5%) of 56 in Norway to 47 (64%) of 74 in Australia (appendix p 4). The proportion of neonates with severe bleeding was similar across all countries (appendix p 4).

Discussion

This multicentre, retrospective cohort study of 389 neonates with FNAIT born in a 10-year inclusion period in seven countries highlights the large variation in contemporary postnatal treatment strategies. Postnatal management strategies included frequent use of matched or unmatched platelets for transfusion, intravenous immunoglobulin, or a combination of treatments. Analysis of one of our outcomes showed differences in platelet count increments between treatment types, with the median platelet increment being significantly increased after matched platelet transfusions than after unmatched platelet transfusions. We could not analyse associations between treatment type and the occurrence of severe bleeding due to missing data on the timing of bleeding. This study presents new information on platelet responses to postnatal treatment for FNAIT, providing a starting point for a comparative clinical trial.

In a previous national cohort study in the Netherlands, we found a great diversity in postnatal treatment strategies for neonates with FNAIT, despite the availability of a national guideline.[11] To our knowledge, this study is the first international study addressing postnatal treatment in neonates affected by FNAIT. More than half of the neonates were postnatally treated with platelet transfusions, which were either HPA-matched, HPA-unmatched, or a combination of both. Differences in treatment strategy might be partly explained by variation in treatment guidelines between centres and in the availability of HPA-matched platelets per country. For example, HPA-matched platelets are not routinely available in many countries (eg, Slovenia) and intravenous immunoglobulin is recommended as a first-line treatment in other countries (including some centres in the USA). Differences in treatment strategy might also be related to variation in the clinical characteristics of the neonates per country, although we did not investigate this possibility.

53% of neonates received platelet transfusions, which is in line with a systematic review reporting that 51% of neonates with FNAIT receive postnatal platelet transfusions.[7] Unmatched platelet transfusion products are often readily available, whereas platelets matched for HPA-1, HPA-5, or both are not always available from hospital stocks or from blood centres due to donor availability and logistical challenges. With HPA-1a positivity being 98% prevalent and HPA-5b positivity being 20% prevalent in the White population,[12] there is a high chance that HPA-unmatched platelet products will be incompatible. Whether matched platelet products yield better clinical outcomes than unmatched platelet products is still unclear. No randomised clinical trials have investigated the differences in clinical outcome and bleeding risk between the two treatments. We observed a significantly larger median platelet count increment in patients receiving matched versus unmatched platelet transfusions. These data confirm the results of previous smaller studies showing that the median platelet increment ranged from 116×10^9 platelets per L to 170×10^9 platelets per L after matched transfusions and from 27×10^9 platelets per L to 68×10^9 platelets per L after unmatched transfusions.[13–16] As in these previous studies, we did not adjust for possible confounding factors between the two groups. However, our cohort had a large sample size and we only used data from first transfusions in patients who received no further transfusions on the same day as the first transfusion or on the following day. First matched platelet transfusions led to larger platelet increments than first unmatched platelet transfusions, but platelet counts after day 3 were similar. However, whether matched platelets better prevent severe bleeding than unmatched platelets remains undocumented. Circulating maternal anti-HLA antibodies in the neonate might also cause the destruction of transfused platelets.[17] These anti-HLA antibodies were not considered in this study.

Approximately a third of neonates received intravenous immunoglobulin postnatally, either alone or in combination with platelet transfusions. Administration

of intravenous immunoglobulin to the mother during pregnancy decreases pathogenic IgG transport from the mother to the fetus due to competition at the receptor level in the placenta and has been shown to reduce the risk of fetal intracranial haemorrhage.[6] The mechanism of action of postnatal intravenous immunoglobulin treatment in FNAIT is not clear. Although our study was not designed to compare the outcomes of treatment regimens, platelet counts in the groups receiving platelet transfusions increased more rapidly than that in the intravenous immunoglobulin only group, in line with previous smaller studies.[18,19]

We found a lower prevalence of severe bleeding (6%) compared with other cohort studies, which have reported rates from 10% to 25%.[5,20] Several explanations are possible. First, we included only liveborn neonates with FNAIT and therefore, unlike other studies, did not include fetuses that had died or pregnancies that had been terminated due to intracranial haemorrhage. As a result, calculating mortality rates was also not possible. Second, about a quarter of neonates in our study received antenatal intravenous immunoglobulin treatment, which could possibly have prevented the occurrence of intracranial haemorrhage. Finally, the definitions of bleeding differed between studies; we classified eight cases of intracranial haemorrhage as mild bleeding, whereas the other studies reported on all neonates with intracranial haemorrhages without stratifying by severity.

In our study, worsening of the intracranial haemorrhage after postnatal diagnosis was reported in only one neonate, suggesting that this event is rare. This finding is consistent with earlier studies suggesting that intracranial haemorrhage develops predominantly during pregnancy rather than postnatally.[21] Given the small proportion of neonates with FNAIT and thrombocytopenia who develop intracranial haemorrhage, it is unlikely that thrombocytopenia is the sole cause of intracranial haemorrhage—another factor might potentially increase the risk of bleeding. In a 2022 cohort study,[22] genetic screening was done in 194 fetuses antenatally diagnosed with intracranial haemorrhage. Pathogenic variants of *COL4A* and *COL4A2* (encoding basement membrane proteins) were found in 36 (19%) of 194 fetuses, emphasising the heterogeneity in the causes of fetal intracranial haemorrhage. Additionally, most HPAs are expressed by endothelial cells.[23,24] Several studies using in-vitro and murine models have shown that anti-HPA antibodies can bind to the endothelium, which might increase the risk of intracranial haemorrhage.[1–3]

This study yielded two additional interesting findings. First, we found an over-representation of male neonates with FNAIT, confirming a similar finding in a previous study.[25] In maternal RhD alloimmunisation, male neonates are also reported to be more severely affected than female neonates.[26] The reason for the difference in sex distribution in neonates affected by FNAIT is not clear. Possible explanations can be found in transplantation medicine. Studies in this field have shown that sex-mismatch is a risk factor for transplant rejection, possibly due to recognition of Y chromosome-encoded peptides by the female immune system.[27] Second, we found that a large proportion of neonates were born small for gestational age, consistent with a previous report.[28] This result could partly be due to selection bias, because additional routine diagnostics tests, including a full blood count, are often done in neonates born with low birthweight, which can lead to the detection of thrombocytopenia. Alternatively, anti-HPA-1a antibodies could have bound to placental cells that express HPA-1a, leading to placental damage and dysfunction and hence fetal growth restriction.[29,30]

There is no international consensus on the optimal postnatal treatment strategy for FNAIT. Different platelet transfusion thresholds and volumes were recommended in the guidelines of the participating centres. The safety and benefits of platelet transfusions in neonates have been questioned after a large, randomised trial in preterm neonates showed that a restrictive transfusion policy (transfusion at $<25\times10^9$ platelets per L) was associated with an improved outcome compared with a more liberal strategy (transfusion at $<50\times10^9$ platelets per L).[31,32] Whether platelet transfusions in neonates with FNAIT could also have deleterious effects is not known and requires further investigation. As shown in this study, platelet counts in most neonates with FNAIT increased to more than 50×10^9 platelets per L in the first week of life. Neonates with FNAIT in the no-treatment group were less likely to have severe disease than those in the treatment groups, because guidelines recommend the administration of platelet transfusions to neonates with very low platelet counts, bleeding, or both. Platelet counts in neonates in the no-treatment group increased spontaneously within the first week of life. None of the 50 neonates with severe thrombocytopenia who did not receive antenatal or postnatal treatment developed bleeding and their platelet count increased spontaneously within the first week of life.

Our study has several limitations. First, the results of our study should be interpreted in light of its retrospective design and probable selection bias, which is highlighted by the small numbers of neonates at several centres. Second, different antibody screening methods were used to detect anti-HPA antibodies. Differences in the sensitivities of these tests might have affected the composition of our cohort.[8] Third, we were not able to analyse the association between bleeding, the time of treatment initiation, and platelet transfusion thresholds, because we could not identify the time of bleeding onset in most neonates. Finally, it is difficult to compare treatment groups owing to confounding by indication, hampering the study of eventual causal effects of the treatments on clinical outcomes. To identify optimal postnatal treatment strategies, information on the timing of the intracranial haemorrhage or other types of severe bleeding in FNAIT is essential. In neonates who develop intracranial haemorrhage postnatally, the time at which

bleeding develops can only be assessed if serial neuroimaging examinations are frequently done throughout pregnancy and throughout the neonatal period. However, because FNAIT is predominantly diagnosed after birth, these data might only become available if a screening programme is in place to detect HPA-alloimmunised pregnancies.

The true effect of different postnatal treatments can only be reliably established with a randomised study design. In the absence of antenatal screening programmes to detect pregnancies at risk of FNAIT in a timely manner, FNAIT is hugely underdiagnosed, hampering recruitment for such a study.[33] However, this large, multicentre, cohort study of neonates with FNAIT evaluated postnatal treatment strategies in seven countries, which varied greatly, provides valuable information for clinicians and researchers on FNAIT treatments and neonatal outcomes, and shows the potential of international collaboration in a future clinical trial. Although our data suggest that HPA-matched transfusions lead to a larger platelet count increment than HPA-unmatched transfusions, whether HPA matching reduces the risk of bleeding is unclear. This study highlights the urgent need for further trials to establish evidence-based guidelines for the management of neonates with FNAIT.

Contributors

TWdV contributed to data curation, the investigation, project administration, and writing the original draft of the manuscript. DW contributed to the investigation and reviewing and editing the manuscript. CC-D contributed to the formal analysis, methodology, and reviewing and editing the manuscript. VA, MZ, VY, and HBCH contributed to the investigation and project administration. JGvdB, DO, CEvdS, MS-V, ET, and EMW contributed to reviewing and editing the manuscript. CCS, ED, HEH, JLK, ZKM, EM-D, NN, LP, MS, and HT contributed to the investigation and reviewing and editing the manuscript. MdH contributed to study conceptualisation and reviewing and editing the manuscript. EL contributed to methodology, supervision, and reviewing and editing the manuscript. TWdV, DW, VA, CCS, ED, HEH, HBCH, JLK, NN, MS, MS-V, LP, ET, HT, VY, and MZ had access to, verified, and interpreted the data of their centre and entered the data into the secured online database. TWdV and CC-D had access to the complete database and verified and analysed the data. All authors read and approved the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

JGvdB reports an unrestricted research grant from Novo Nordisk and previous payment for teaching by Bayer, both of which were paid to their institution. DO is funded as a research consultant by Janssen Pharmaceuticals and participates on the advisory board of Janssen Pharmaceuticals. HT reports previous payment from Prophylix related to a patent on a monoclonal anti-HPA-1a antibody, is funded as a research consultant by Janssen Pharmaceuticals (as of Aug 1, 2021), and will be a local study site principal investigator in a planned multicentre natural history study on FNAIT sponsored by Rallybio. ET and EL report consultancy fees from Janssen Pharmaceuticals for participating on the advisory board on FNAIT. All other authors declare no competing interests.

Data sharing

Requests for the deidentified data used in our analyses can be sent to the corresponding author, beginning 3 months and ending 36 months after publication of this Article, and will be reviewed by the scientific committee of the initiating centre and the primary investigators of the participating centres. If approval is given, data will be shared through a secure portal. The study protocol will be made available upon reasonable request to the corresponding author.

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