Antigen-positive platelet transfusion in neonatal alloimmune thrombocytopenia (NAIT)

Volker Kiefel¹, Dirk Bassler², Hartmut Kroll³, Bosco Paes², Günter Giers⁴, Juliana Ditomasso⁵, Heidemarie Alber⁶, Monika Berns⁷, Bea Wiebe⁸, Ernst-Markus Quenzel⁹, Jochen Hoch¹⁰, Andreas Greinacher¹¹

Short title: Incompatible platelet transfusion in NAIT

¹Department of Transfusion Medicine, University of Rostock, Germany, ²Departments of Pediatrics (Neonatology Division) and ⁵Transfusion Medicine, McMaster University, Hamilton, Canada, ³German Red Cross Blood Transfusion Service, Dessau, Germany, ⁴Institute for Transfusion Medicine and Hemostaseology, University of Düsseldorf, Düsseldorf, Germany, ⁶Institute for Transfusion Medicine, German Red Cross Blood Transfusion Service, Dresden, Germany, ⁷Department of Neonatology – Otto Heubner Centre, Charité Campus Virchow, Berlin, Germany, ⁸Department of Neonatology and Pediatric Intensive Care, Asklepios Clinic, St. Augustin, Germany, ⁹Department of Transfusion Medicine, Helios Clinic, Schwerin, Germany, ¹⁰Institute for Experimental Hematology and Transfusion Medicine, University of Bonn, Germany, ¹¹Institute for Immunology and Transfusion Medicine, University of Greifswald, Germany

This study has been supported by the German Federal Ministry of Education and Research (CAN04/006; NLB3 program ref 01-ZZ0403)

Corresponding author:
Volker Kiefel, M.D.
Department of Transfusion Medicine
University of Rostock
Ernst-Heydemann-Strasse 6
D-18057 Rostock, Germany
Mail: volker.kiefel@med.uni-rostock.de
Phone: +49 381 494 7680
Fax: +49 381 494 7694

Word count (text): 1185
Word count (abstract): 138

Keywords: neonatal alloimmune thrombocytopenia, cerebral hemorrhage, anti-HPA-1a, platelet transfusion

Scientific heading: Transfusion Medicine
Abstract

Neonatal alloimmune thrombocytopenia (NAIT) is a fetomaternal incompatibility, most commonly induced by maternal anti-HPA-1a, IgG alloantibodies against a polymorphic epitope of the glycoprotein IIb/IIIa complex, in approximately 97.5% of Caucasians. Current guidelines recommend transfusion of immunologically compatible platelets to prevent cerebral hemorrhage, the most severe complication in affected newborns. Such platelet concentrates, however, are often not readily available. In a retrospective analysis in German and Canadian centres, twenty-seven newborns with NAIT were identified who received platelets from random donors. Unexpectedly, 24/27 newborns showed an increase above a threshold of 40 x 10^9 platelets/L, with moderate (n=8) or significant (n=16) platelet count increments (> 80 x 10^9 platelets/L). We conclude that transfusion of platelet concentrates from random donors is an appropriate strategy in the management of unexpected, severe NAIT predominantly in first pregnancies, pending the availability of compatible platelets.
Introduction

Neonatal alloimmune thrombocytopenia (NAIT) is an immune mediated fetomaternal incompatibility. It occurs after maternal alloimmunization against polymorphic epitopes on fetal platelet glycoproteins (GP) and diaplacental transfer of maternal IgG alloantibodies to the fetus. Alloantibodies implicated in NAIT are directed against antigens on GP IIb/IIIa, Ib/IX, Ia/IIa, and CD109. The most common antibody is anti-HPA-1a (originally referred to as anti-Zw(a)^1\(^\), which accounts for about 75 percent of cases.\(^2\) A leucine-proline polymorphism of GP IIIa of amino acid 33 is the molecular basis of the HPA-1a/1b-polymorphism.\(^3\) NAIT has an incidence of 1:1000 to 1:2000 births in Caucasian populations and may occur if a pregnant, HPA-1b/1b homozygous woman is immunized with HPA-1a-positive platelets by her fetus.\(^4\)-\(^5\)

NAIT is a self-limiting and transient disorder with an excellent prognosis in the absence of cerebral bleeding. Approximately 42% of newborns with NAIT are born to primiparous women.\(^6\) Prenatal screening for maternal platelet-specific alloantibodies has not been established\(^5\) and the birth of a first affected child therefore occurs unexpectedly. As a significant proportion of untreated newborns with NAIT (approximately 7 to 14%\(^6\)-\(^7\)) are affected by cerebral hemorrhage in the first days of life, a liberal attitude towards platelet transfusion of the severely thrombocytopenic newborn is considered appropriate.\(^8\) While intravenous gamma-globulin (IVIG) has been shown to be of some benefit in the antenatal management of alloimmune thrombocytopenia,\(^9\) high-dose IVIG can only be recommended as a complementary treatment modality in the management of NAIT because of the delayed rise in platelet counts and limited evidence from a small series of cases.\(^10\)-\(^11\) Currently, antigen-negative platelets are considered optimal for the prevention of hemorrhage in newborns with suspected NAIT.\(^8\),\(^12\) To meet this need, transfusion services have attempted to stock HPA-1a negative and HPA-5b negative donor platelet
concentrates for emergency use. However, this remains a logistic challenge, given the relatively low frequency (approximately 2.5 percent) of HPA-1a negative donors.\textsuperscript{12} As an alternative to HPA-1a negative donor platelets, transfusion of maternal platelets is recommended.\textsuperscript{13} However, these platelets must also be prepared within a short time and the appropriate facilities are available 24 hours a day only in specialized centers. In addition, maternal platelet concentrates have to be processed in order to remove maternal antibodies, tested for transfusion-relevant infection markers and irradiated. Therefore, in cases of unexpected NAIT, maternal platelet concentrates are only available after a delay of 12 to 48 hours.

While awaiting the arrival of compatible platelets, newborn babies with alloimmune thrombocytopenia due to maternal anti-HPA-1a have been transfused with random donor platelets and in some cases unexpected high platelet increments have been observed.\textsuperscript{14-17} To study more systematically the effect of HPA-1a incompatible platelet transfusions in severe NAIT, we initiated a review of newborns with severe NAIT who received random donor platelet concentrates.

**Methods**

In this retrospective analysis we enrolled six German and one Canadian university hospitals (Berlin, Bonn, Düsseldorf, Giessen, Greifswald, Hamilton, Rostock) and one German Red Cross transfusion laboratory (Dresden). Each center identified platelet transfusions in NAIT patients who fulfilled the following criteria: 1. laboratory confirmed HPA-1a antibodies in maternal blood samples, 2. transfusion of platelet concentrate(s) from random donors, 3. a period of observation of four days or longer with documented platelet counts. Platelet transfusions and other therapeutic interventions aimed at
preventing bleeding complications, platelet counts, and response to platelet concentrate transfusions were retrieved from each patient's file. Platelet antibodies were detected using glycoprotein specific assays.\textsuperscript{18}

**Results and Discussion**

Twenty-seven neonates (11 female, 16 male) born to mothers with serologically confirmed HPA-1a antibodies were identified (figure 1, 2), who received at least one HPA-1a positive (patient number 1-3, 5, 8-11, 13) or random platelet concentrate. Maternal antibody status was known in 5/27 cases, median gestational age was 39 weeks, 25\textsuperscript{th} quantile 37.5, 75\textsuperscript{th} quantile 39.5 weeks. Thirteen of 26 newborns were born to primiparous women. In all but three patients (7, 20, 24), platelet counts increased above $40 \times 10^9$/L following 1-2 random platelet transfusions, a value above the threshold of $30 \times 10^9$/L considered relevant in the prevention of cerebral hemorrhage.\textsuperscript{8} After the first 1-2 transfusions, significant increments (more than $80 \times 10^9$/L) were observed in 16/27 patients (1-3, 5, 6, 10-15, 17, 21, 23, 25, 26) and less pronounced, but still sufficient increments in patients 4, 8, 9, 18, 19. Even patient 16, the second of two siblings with severe NAIT, who was born with a platelet count of $6 \times 10^9$/L, and who showed a minor increment still did not require further transfusion. Response to four random platelet transfusions was highly variable in patient 22. There were three exceptions in this series of patients: in patient 7, 20 and 24 random donor platelets were clearly without effect, and further HPA-1a-negative platelet transfusions were required in patients 7 and 20. Ten patients also received IVIG (1, 6-7, 13, 16, 20-22, 24, 25) and four patients were treated with corticosteroids (4, 7, 19, 22). In none of the patients, adverse effects related to random donor platelet transfusions (e.g. DIC or increased hemorrhage) were observed. Cerebral hemorrhage occurred prenatally in patients 1, 6, and in patient 5, hydrocephalus of unknown aetiology was diagnosed at birth.
underscoring the severity of NAIT.

The cause for the relative effectiveness of immunologically incompatible platelet transfusion in NAIT is not entirely clear. Potentially a sufficiently large dose of antigen-positive platelets might adsorb circulating alloantibodies and thus enhance recovery of megakaryocytes and thrombocytopoiesis. This could explain the observation of a delayed rise in platelet counts in some patients. From an immunologic perspective, a newborn, who has been sensitized by alloantibodies as result of passive transplacental transfer, may react more favourably when transfused with antigen-positive platelets than an actively immunized subject. The likely explanation is that the incompatible transfusion in the situation of passive immunization will not enhance the antibody titer.

In our study we found that in 24 out of 27 newborns with unexpected severe NAIT transfusion of a random platelet concentrate led to an increase in platelet count sufficient for the prevention of spontaneous cerebral hemorrhage. This and the fact that transfused babies experienced no serious adverse effects strongly indicates that immediate transfusion of a random platelet concentrate in severe, unexpected NAIT may be associated with fewer risks than waiting for several hours or even days for a HPA-compatible platelet concentrate. Our study clearly demonstrates that a positive response to antigen incompatible platelets does not exclude NAIT and confirms observations by Bussel et al. 19 Although the cases described in this manuscript may not include all presentations of NAIT, they lend credence to the fact that transfusion of antigen-positive platelets is a definite treatment option in NAIT following maternal HPA-1a alloimmunization.

In conclusion, we recommend the use of random platelet concentrates in newborns
suspected to have NAIT with platelet counts below 30 x 10^9/L while waiting for matched (HPA-1a(-), HPA-5b(-)) platelets, if these are not immediately available. One might speculate that transfusion of antigen-positive platelets will shorten the thrombocytopenic period, if adsorption of alloantibodies is the major mechanism. A randomized controlled trial to support the efficacy and safety of this strategy is awaited and the benefits of concomitant administration of IVIG remains to be demonstrated.

Acknowledgements:

This study has been supported by the German Federal Ministry of Education and Research (CAN04/006; NLB3 program ref 01-ZZ0403). The greatest group of patients was contributed by H. Kroll, MD (Giessen, Germany, now located at German Red Cross Transfusion Service, Dessau, Germany).
References


[14] Win N. Provision of random-donor platelets (HPA-1a positive) in neonatal alloimmune


Figure 1: Platelet count and therapy in cases no 1 to 13. HPA-1a-positive platelet transfusions are indicated by black, HPA-1a-negative transfusions by gray arrows with round heads. IVIG infusions are indicated by triangles, single doses of corticosteroids by squares. Newborns with platelet counts below $30 \times 10^9/L$ (area shaded in gray) are considered to be at enhanced risk for major hemorrhage.

Figure 2: Platelet count and therapy in cases no 14 to 27. HPA-1a-positive platelet transfusions are indicated by black, HPA-1a-negative transfusions by gray arrows. IVIG infusions are indicated by triangles, single doses of corticosteroids by squares.
Figure 2
Antigen-positive platelet transfusion in neonatal alloimmune thrombocytopenia (NAIT)

Volker Kiefel, Dirk Bassler, Hartmut Kroll, Bosco Paes, Gunter Giers, Juliana Ditomasso, Heidemarie Alber, Monika Berns, Bea Wiebe, Ernst-Markus Quenzel, Jochen Hoch and Andreas Greinacher