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CASE STUDY

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Acute haemolytic transfusion reaction after transfusion of fresh frozen plasma in a neonate—Preventable by using solvent/detergent-treated pooled plasma?

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Abstract

Background: Plasma is a commonly used blood product and is available in the form of fresh frozen plasma (FFP) or pooled solvent/detergent-treated plasma. In the Netherlands, solvent/detergent-treated plasma has become the standard product in the adult population since several years, but for neonatal use, FFP remains the product of preference.

Description: A preterm neonate developed lung bleeding at day 8 postpartum, for which intubation and mechanical ventilation was required and transfusions with packed red blood cells and plasma, in the form of FFP, were given. Five hours after transfusion, a red discoloration of the urine occurred. An acute haemolytic transfusion was suspected, confirmed by laboratory investigations (fast decrease in haemoglobin, increased free haemoglobin, decreased haptoglobin, increased lactate dehydrogenase and a positive direct antiglobulin test [IgG 2+]). Additional research showed that the FFP product contained nonspecific auto-antibodies that reacted with the transfused erythrocytes, most test erythrocytes and the donor's own erythrocytes.

Conclusion: A neonate experienced an acute haemolytic reaction, most probably caused by administrating a FFP product containing auto-antibodies. If transfused with solvent/detergent-treated plasma, such antibodies would have been diluted or captured. This case adds a new argument to the discussion on expanding the use of solvent/detergent-treated plasma to the paediatric population.

KEYWORDS
fresh frozen plasma, neonatal transfusion, solvent/detergent-treated plasma, transfusion reaction

1 | INTRODUCTION

Plasma is a commonly used blood product, mainly for treatment and prevention of bleeding in patients with coagulopathy and as replacement fluid in plasma exchange.[1] In the Netherlands, around 60 000 units of plasma are transfused annually.[2] Plasma products include fresh frozen plasma (FFP) and pooled solvent/detergent-treated plasma (SD plasma). FFP is a product derived from a single donor, while SD plasma is a product made by pooling several hundreds of plasma units.[3] In the Netherlands, SD plasma (Omniplasma®, made from Dutch donor plasma, manufacturer: Octapharma, Austria) has become the standard product in plasma transfusion and plasma exchange for adults since 2014. However, for neonatal use FFP is still the product of first choice. This is mainly caused by two reasons. First, there is limited evidence of SD plasma in neonatal use. There are no large high-quality randomised controlled trial available comparing efficacy and safety of FFP to SD plasma products, specifically in children. The evidence available consists of smaller or observational studies investigating SD plasma in paediatric use.[4–8] Due to this limited evidence, the product information of SD plasma states that experience with use in children is limited.[9] However, it should be noted that high-quality large trials for FFP in paediatric or neonatal use are lacking as well, but the main difference is that FFP is not registered as drug, and therefore stricter regulations apply for SD plasma. The second reason for preference of FFP over SD plasma is related to the costs and volume of the plasma products. FFP is available in both 150 and 300 mL, and preterm neonates generally need a volume lower than 150 mL, so the smaller (and cheaper) product is sufficient. SD plasma is available in only 200 mL, which has the same price as 300 mL FFP. Therefore use of SD plasma for neonatal use would result in higher costs. A Canadian study investigating cost-effectiveness of SD plasma and FFP, also showed that replacement of all FFP by SD plasma would increase costs with $16.5 million per year.[10]

However, we question if the preference of FFP over SD plasma is correct. We describe a case in which FFP was administered to a neonate, resulting in a transfusion reaction. In our opinion, this transfusion reaction would most likely not have occurred if SD plasma had been given to this patient, therefore we advocate for considering expanding the indication of SD plasma and include paediatric and neonatal use.

1.1 | Patient and clinical information

A preterm neonate, born after 28 + 5 weeks of pregnancy and part of a dichorionic twin pair, had a uncomplicated clinical course during the first week after birth. However, at day 8 postpartum lung bleeding of unknown aetiology occurred, for which intubation and mechanical ventilation was required and transfusion with packed red blood cells (pRBCs) (15 mL kg^{-1}) was given. Given the acute bleeding and abnormal coagulation parameters, vitamin K and plasma, in the form of FFP, (15 mL kg^{-1}), were given. The activated partial thromboplastin time and haemoglobin value improved after the transfusion of pRBCs and plasma (Table 1). However, 5 h after transfusion, discoloration of the urine into red/reddish brown urine started, which lasted for 1 day. The patient also experienced a mild rise in body temperature (38.2°C). Based on these symptoms, the occurrence of an acute haemolytic transfusion reaction was suspected, and additional laboratory measurements were performed (Table 1). The decreased haptoglobin, increased free haemoglobin, the increase in lactate dehydrogenase and the fast decrease in haemoglobin from 7.7 mmol L^{-1} (12.4 g dL^{-1}) just after the transfusion to 6.6 mmol L^{-1} (10.6 g dL^{-1}) the day

TABLE 1 Laboratory values of patient around time of lung bleeding and transfusion

Laboratory value	Day 8 postpartum (in evening lung bleeding and transfusion)	Day 9 postpartum	Reference value
Haemoglobin[a]	4.6 → 7.7[b] [7.4 → 12.4[b]]	6.6 [10.6]	7.5–10.0 mmol L^{-1} [12.1–16.1 g dL^{-1}]
LDH	415[e]	1286	<600 U L^{-1}
Haptoglobin	–	<0.1	Unknown in children <1 year 0.3–2.0 g L^{-1} for age > 1 year
Free haemoglobin	–	28	<2 μmol L^{-1}
Total bilirubin[a]	86 → 100[b]	160	<17 μmol L^{-1}
APTT	88.0	45.2	26.9–74.1 s[d]
PT	18.9	21.6	10.0–15.3 s[d]
Fibrinogen	2.6	3.9	1.6–4.2 g L^{-1}[d]
Direct antiglobulin test	Negative[c]	Positive (IgG 2+)	Negative

Abbreviations: APTT, activated partial thromboplastin time; LDH, lactate dehydrogenase; PT, prothrombin time.

[a]Measured in an arterial blood gas syringe.

[b]First value is before transfusion of packed red blood cells, second value after transfusion.

[c]Reference values for healthy preterm neonates at day 5. These reference values are used at the neonatology department and are derived from Andrew et al.[11]

[d]Result of this direct antiglobulin test is before transfusion of blood products.

[e]Measured at day 7 postpartum. No measurement from day 8 postpartum.

after transfusion were suggestive for a haemolytic reaction. In the urine sediment, no intact erythrocytes were seen, ruling out a nephrological or urological cause for the discoloured urine. Since the raised body temperature could possibly be attributable to a bacterial infection, broad-spectrum antibiotic treatment was started and stopped after 3 days when bacterial cultures turned out negative.

The patient recovered after the lung bleeding and haemolytic reaction, however at day 15 postpartum another lung bleeding occurred. At this time no deviations in coagulation parameters were apparent, but a repeated plasma transfusion was given, together with an pRBC transfusion. Haemoglobin concentration increased from 5.1 mmol L^{-1} (8.2 g dL^{-1}) to 7.4 mmol L^{-1} (11.9 g dL^{-1}) without any clinical signs of a subsequent transfusion reaction.

The aetiology of the lung bleeding was unknown and was considered to be most likely related to the prematurity of the patient or the patent ductus arteriosus that appeared to be present at day 8 after birth. A CT scan of the lungs did not show any abnormalities. The twin sibling also experienced a bleeding (stomach bleeding), therefore a hereditary coagulation disorder was considered as well. However, as coagulation parameters were not aberrant during the second bleeding, and there was no family history of coagulation disorders, this was considered unlikely. At the age of 7 months, Von Willebrand disease was investigated for both siblings, but results showed no abnormalities. The twins did not experience an increased bleeding tendency anymore and were in good health.

1.2 | Laboratory investigations of transfusion reaction

After suspicion of the acute haemolytic transfusion reaction, additional laboratory investigation with a blood sample of the patient, drawn after the reaction, and material of the transfused blood products was performed. The direct antiglobulin test (DAT) of the neonate was positive for IgG 2+. In comparison, a DAT performed on the day of birth was negative. Although the DAT was positive, the eluate by both freeze and acid elution methods did not show any reactions against reagent red cells. AB0-antagonism was ruled out (the mother was A positive, neonate AB positive, transfused pRBCs 0 negative and transfused FFP AB positive). No anti-A or anti-B IgG antibodies were shown for the mother. Additional research with a blood sample from the mother of the neonate was performed to investigate if maternal antibodies transferred during pregnancy could have caused a transfusion reaction. However, a screening panel of the mother was negative and cross-matching of the transfused pRBCs with plasma of the mother did not produce a positive reaction.

As the laboratory tests in the hospital laboratory did not result in an explanation for the transfusion reaction, additional investigation on the transfused products was performed at the national immunohematology reference laboratory of the Netherlands (Sanquin Diagnostic Services, Amsterdam, the Netherlands). Here, serologic analysis was performed with samples of the same FFP-donor and fresh blood samples of the pRBC donor. A blood sample of the patient was not available anymore. The tests exposed that there were antibodies present in plasma of the FFP donor. The antibodies reacted with the erythrocytes of the pRBC donor, but also with most test erythrocytes (reagent cells) in LISS column agglutination techniques. The DAT of the erythrocytes from the FFP-donor was positive with anti-IgG (2+) while acid elution resulted in weak reactions with reagent cells in LISS column agglutination techniques. The antibodies of the FFP donor were considered to be nonspecific auto-antibodies. Other FFP units from this donor were recalled by Sanquin Blood Bank, and samples from these products showed the same reactivity. No transfusion reactions were reported for the already transfused FFP units. The FFP donor had no signs of haemolysis. The screening for RBC antibodies at the time of the first donation was negative. According to the Dutch guidelines there was no screening for RBC antibodies performed on the current donation.

2 | DISCUSSION AND CONCLUSION

In this report we describe a neonate that developed an acute haemolytic reaction, with red discoloured urine, which was possibly caused by transfusion of a FFP product containing auto-antibodies. These weak autoantibodies of the FFP donor caused acute haemolysis presumably of the transfused donor erythrocytes after both products were transfused.

Published literature reviews and guidelines show that studies to guide plasma use in neonates are limited. There is no clear evidence for prophylactic plasma transfusions to neonates with abnormal coagulation values.[12–14] In the neonatal intensive care unit where the patient in this case report was treated, the use of plasma transfusions decreased significantly over the years (analysed between 2004 and 2019).[15]

FFP is in the Netherlands a product derived from a single donation of male donors. The FFP product is frozen within 24 h after collection and then stored frozen for a period of at least 6 months after which it can be released if tests for blood transmittable infectious diseases for the donor are negative after the second donation. Male-only plasma is used since 2007 to reduce the risk of transfusion-related acute lung injury caused by anti-human leukocyte antigen and/or neutrophil antibodies which are more prevalent in the female population.[16]

SD plasma is a product in which plasma from 600 to 1200 donors is pooled. The pooling of hundreds to thousands of single-donor plasma units, reduces neutralising antibodies present in the plasma pool through dilution, lowers the antibody titres against blood cells and plasma proteins, resulting in an improved safety profile.[3,4] The manufacturing process includes several steps to remove pathogens: by a solvent/detergent treatment enveloped viruses are eliminated, and by filtration with nanofilters the non-enveloped blood transmittable infectious diseases including prions are removed, except for very small non-enveloped viruses such as Parvo B19. This is monitored by PCR-testing of batches.[3] Due to this pooling, SD plasma has a standardised content of plasma proteins, in contrary to FFP plasma, which is prone to interindividual differences between donors. A drawback is that SD plasma had reduced protein S concentrations compared with

FFP, which can contribute to risk of thrombosis in patients receiving large volumes for plasma exchange.[17]

Arguments against the use of SD plasma in neonatal or paediatric care is due to limited literature evidence for the use of SD plasma in children, and therefore is not included for paediatric indications in the drug label. In addition, due to the pooling, multiple donor exposure in neonates can result in increased risk of adverse effects like transfusion transmitted infections and immunomodulation.[18]

Although literature evidence of SD plasma in children is limited, there are several published studies. In a large prospective observational study the use of FFP and SD plasma were compared in critically ill children in 101 paediatric intensive care units in 21 countries.[4] 419 paediatric patients (median age 1 year, interquartile range 0.2–6.4 years) were included, of which 357 received FFP and 62 SD plasma. ICU mortality was lower in the patient group treated with SD plasma (14.5%) compared with the FFP group (29.1%, $P = 0.02$). The effect on the coagulation parameter international normalised ratio (INR) was comparable for both groups (in both groups a reduction of 0.2 of the INR, $P = 0.80$).[4]

A retrospective study investigated paediatric cardiac surgical patients that were aged below 2 years and less than 10 kg (undergoing complete tetralogy of Fallot repair), that received either FFP or SD plasma (OctaplasLG) during surgery.[7] The study included 105 patients over a 10-year period, of which 5 years of FFP use and 5 years of SD plasma use. The study showed that SD plasma was as effective in achieving haemostasis as FFP.[7]

In a recently published phase IV study in which the safety, tolerability and efficacy of SD plasma (Octaplas) was investigated, 50 patients aged <16 years were included, of which 37 were 0–2 years old.[5] No hyperfibrinolytic or thromboembolic events or adverse drug reactions were reported after transfusion of SD plasma. Although a relatively small study population, this study suggests that SD plasma can be used safely in this paediatric population.[5]

The patient described in this report experienced an acute haemolytic reaction, possibly related to FFP. In general, an acute haemolytic reaction on FFP is very rare. In 2019, 17 events of an acute haemolytic transfusion reaction were reported in the Netherlands, but non-related to a plasma product (16 related to a red cell product, 1 to a platelet transfusion).[2]

For neonatal transfusions, it can also be considered to perform minor cross-matching (i.e. combining donor serum and recipient red blood cells), which can prevent incompatibilities and transfusion reactions such as described in this case. Minor cross-match is however not standard practice in the Netherlands for (neonatal) plasma transfusions. As long as the unit of plasma is ABO compatible with the recipient and plasma of the donor is screened for unexpected non-ABO antibodies a minor cross-match is not required. We did consider a retrospective minor cross-match with the FFP donor in this case, but unfortunately there was no blood sample left of the recipient. More regular antibody screening of the FFP donor could perhaps also have prevented this problem, but currently, according to Dutch guidelines, only first donations are screened for RBC antibodies.

In the Netherlands, SD plasma is generally not used in a paediatric population. Therefore, the neonate in this case was given a plasma transfusion with FFP, according to standard of care. Also in guidelines for neonatal transfusion in the United Kingdom, only use of FFP is recommended.[19] We believe that the transfusion reaction most likely would not have happened if SD plasma would have been given to this patient, as antibodies such as the ones present in the FFP donor in this case are diluted in pooled SD plasma. This case adds a new argument to the discussion on expanding the use of solvent/detergent-treated plasma to the paediatric population.

AUTHOR CONTRIBUTION

None.

CONFLICT OF INTEREST

The authors have no competing interests.

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