CASE REPORT

Intravenous iron administration together with parenteral nutrition to very preterm Jehovah's Witness twins

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SUMMARY

Preterm twin sisters (monozygotic) were born at gestational age 27 weeks and 5 days with birth weights of 935 and 735 g. They were admitted to our neonatal intensive care unit for a period of 1 month. Their parents were Jehovah's Witnesses and refused blood transfusion for their preterm daughters. Subcutaneous erythropoietin and intravenous iron were given as a prophylactic to avoid anaemia.

BACKGROUND

Infants with birth weights <2000 g require iron supplementation of 2–3 mg/kg/day according to the recommendation from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) committee.[1] These preterm infants should start prophylactic enteral iron supplementation (given as a separate iron supplementation in preterm formula or in fortified human milk) at 2–6 weeks of age and continue with 0.9–1.3 mg/kg/day from 6 to12 months of age depending on diet (as the recommendation for mature infants).

Infants with significant blood losses or infants in erythropoietin treatment may need a higher dose of iron supplementation. If iron supplementation is too high there is a possible risk of retinopathy of prematurity or oxidative injury, and therefore doses above 5 mg/kg/day should be avoided.

Very-low-birth-weight infants do not routinely receive intravenous iron supplementation because usually the iron need will be met with red blood cell transfusions.

Also, there have been concerns about the risk of the trivalent cations (Fe^{3+}) that possibly can destabilise lipid emulsions in all-in-one parenteral solutions.[2] Based on expert opinion from 1988, there is a recommendation of intravenous iron of 200 μg Fe/kg for infants receiving total parenteral nutrition (TPN),[3] while two newer papers based on clinical trials suggest higher doses of intravenous iron of 1000 μg/kg/day for preterm infants receiving total parenteral nutrition.[4 5]

Receiving blood products is a conflicting issue for Jehovah's Witnesses because of their religious belief; they also refuse blood transfusions for their children. Our healthcare system does not contain national guidelines or instructions on how to handle these ethical dilemmas. There have been case reports on handling severe anaemia in Jehovah's Witness preterm babies which describe different treatments and approaches.[6 7] In order to give blood transfusion, the hospital department can choose to make the baby a ward of court. Or, in the process of avoiding the need of blood transfusion, the medical staff may consider giving the preterm infants erythropoietin, parenteral and/or enteral iron and vitamin supplementations and furthermore try to maintain a strict blood sampling control.

CASE PRESENTATION

The mother was third time pregnant, giving birth for the third time and both parents were Jehovah's Witnesses. Owing to twin-to-twin transfusion syndrome, a caesarean section was performed at gestational age (GA) 27 weeks and 5 days. Two girls were born. Twin A was small for gestational age with a birth weight (BW) of 735 g (−3.2 SDS) while twin B (the recipient) had a BW of 935 g (−1.8 SDS).[8]

Both girls developed respiratory distress syndrome. Primarily they were stable and treated with nasal continuous positive airway pressure (N-CPAP), but both increased in oxygen support and were treated with surfactant. Both twins were mechanically ventilated; twin A for 8 days and twin B for 14 days. Twin B developed a unilateral intraventricular haemorrhage (IVH) stage 2 while twin A had no IVH. Both girls had persistent ductus arteriosus (PDA) and were both treated twice with Pedea (Ibuprofen) with no effect on closing the PDA.

To avoid red blood cell (RBC) transfusions there was a strict control of blood sampling. Nevertheless, twin A received one blood transfusion 3 days after birth due to a decrease in haemoglobin to 5 mmol/L and being clinically unstable (including hypotension already treated with dopmin). In this situation, the girl was made a ward of court and treated with a red blood cell transfusion.

The parents were very eager to start treatment with erythropoietin (EPO), intravenous iron, vitamin B_{12} (cobalamin) and folic acid shortly after birth. Prophylactic treatment with subcutaneous NeoRecormon (Epoetin β) (250 IE/kg three times each week)[9] was started on day 3 (table 1). The girls were enterally fed with small amounts of mother's milk but were mainly treated with parenteral nutrition during the first weeks of life. The parenteral nutrition contained Vitalipid, Peditrace and Soluvit. The latter with folic acid and cyanocobalamin (vitamin B_{12}).

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Table 1 Prophylactic treatment to avoid anaemia in preterm twins

	Birth	Day 3	Day 3	Day 4	Day 15	Day 18	Day 28
Twin A	PN intravenous	+EPO subcutaneous	RBC-Tr	+CosmoFer intravenous infused together with PN	sep PN sep CosmoFer intravenous +Glycifer orally +FolicAcid orally	–	Lophacomb B_{12} subcutaneous
Twin B	PN intravenous	+EPO subcutaneous	–	+CosmoFer intravenous infused together with PN	CosmoFer intravenous infused separately	sep PN sep CosmoFer +Glycifer orally +Folic acid orally	Lophacomb B_{12}subcutaneous

EPO, erythropoietin; PN, parenteral nutrition; RBC-Tr, red blood cell transfusion; sep, seponation.

Parenteral iron treatment was not used as a routine in our neonatal intensive care unit, and according to guidelines enteral iron supplementation would usually not be initiated until 4 weeks after birth. We wanted to meet the parents' wishes, parenteral infusion with CosmoFer (Iron (III)-hydroxide dextran complex) was initiated on day 4.

By mistake CosmoFer was infused (1.5 mg/day) together with parenteral nutrition for 10 days, and was terminated together with parenteral nutrition when twin A was fed only enterally and did not require parenteral nutrition anymore. Twin B received parenteral nutrition for 13 days, but CosmoFer was given as a separate 4 h infusion (1 mg (0.02 mL of 50 mg/mL)) diluted with 4 mL saline for the past 3 days.

Glycifer (Ferrous glycine sulfate) was initiated in a low daily enteral dose (3 drips of 30 mg/mL) on days 15 and 18 (usually 5 drips are initiated at 4 weeks of age). Folic acid was also initiated enterally on days 15 and 18 with a daily dose of 0.25 mg/kg/day (solution for infusion and injection 10 mg/mL). The twin girls' levels of S-ferritin were never measured.

Vitamin B_{12}/cobalamin was acquired as Lophacomb-B_{12} Depot (cyanocobalamin) and initiated on day 28. Lophacomb-B_{12} was given as subcutaneous injections with 100 µg (0.2 mL of 1000 µg/2 mL) and continued every third month after hospital discharge.

Enteral supplementation with phosphate was initiated on day 8, and vitamin supplements (multivitamin Duplo made by the hospital pharmacy with vitamin A, B, C and E and folic acid) were initiated on day 24. The girls were fed with their mother's milk supplemented with human milk fortifier (Enfamil).

During the hospital admission the twin girls received prophylactic antibiotics intravenously initially due to culture confirmed group B streptococci and *Escherichia coli* in the mother's urine before birth. Later, twin A developed a sepsis due to a central venous catheter infection (confirmed coagulase-negative staphylococci in the blood culture) and was treated with antibiotics.

OUTCOME AND FOLLOW-UP

The girls were clinically stable in N-CPAP on day 30 and were transferred to a neonatal/paediatric department at a hospital near their hometown. They were 32 weeks postmenstrual age when transferred, twin A weighed 960 g and twin B 1243 g. The twins did not develop retinopathy of prematurity (ROP). The parents did not reject twin A due to the red blood transfusion, and they maintained a good relationship with the medical and nursing staff.

DISCUSSION

There are no guidelines in Denmark on how to manage preterm Jehovah's Witness babies with severe anaemia. Standard practice in our neonatal unit is to give RBC transfusion when haemoglobin is below 8 mmol/L, the patient is mechanically ventilated (FiO_2>0.30), is less than 28 days old and has clinical signs of cardiovascular compromise.

Patients receiving long-term parenteral nutrition are recommended to receive iron supplementation.[10] The recommended iron dose for preterm infants is 200 µg/kg/day.[3] The very-low-birth-weight infants need supplemental iron to increase their low iron stores and to increase their erythropoiesis. Supplementary iron enhances growth rate in preterm infants and can be provided in order to avoid recurrent need of RBC transfusions. It is not standard practice to give intravenous iron to preterm babies, and one should consider the known risks such as ROP/oxidative injury, unknown risks (not reported/published) and unexpected risks (due to unfamiliar practice).

The medical staff in our unit was met with the dilemma of meeting the parents' wishes and the interests of the children. We wanted to meet the parents' wishes as much as possible in our family-oriented care treatment. As recommended we consider parents having legitimate interests after birth like fetuses having legitimate interests before birth.[11] It is important to consider what is 'in the best interest of the children',[12] and part of this is to get parents' commitment and acceptance of the children and the children's condition. This is fundamental in the parent–child relationship and will help the children in the long term.[13]

In our case, twin A, who was ventilated, had a gradual decrease in haemoglobin from 8.2 to 5 mmol/L and she was clinically unstable (hypotension treated with dopmin). We therefore decided to make her a ward of court and treat her with an RBC transfusion. The parents did not reject twin A despite the blood transfusion.

Subcutaneous NeoRecormon (Epoetin β) (250 IE/kg three times weekly) was started on day 3. Prophylactic administration of human recombinant erythropoietin before 8 days of age has shown a small reduction in the need of blood transfusions.[14] On the other hand, the authors of the Cochrane review 2012 do not recommend early administration of EPO because there are limited benefits and an increased risk of ROP (stage >3). The twins in our case did not develop ROP.

Vitamin B_{12} and folic acid were started on day 28 as these vitamins have been shown to improve erythropoiesis in the treatment of anaemia of preterm infants.[15]

CosmoFer was added to the parenteral nutrition. The parenteral nutrition solution used in our cases was manufactured by the hospital pharmacy on the basis of a Statement on Stability made by Fresenius Kabi though lacking compatibility data for adding iron. Seemingly, our twins did not get any side effects.

Iron dextran is not recommended to be added to lipid emulsions or all-in-one parenteral mixes because the trivalent cations (Fe^{3+}) can destabilise the negative surface charge between lipid particles. The impact can unite small lipid particles and form large particles.[2] Driscoll *et al*[16] showed that the trivalent cation

in iron dextran could interfere with lipid-based parenteral nutrient mixtures and increase the fat particle size which may be potentially dangerous. One could imagine that these large lipid droplets could cause fat emboli in human organs, especially in neonates. Puntis and Rushton found intravascular lipids in the small pulmonary capillaries in 15 live born infants at necropsy. This group had received significantly more fat during parenteral nutrition (total amount g/kg and number of days) compared with another group of 15 infants who did not have lipid staining. However, the authors found no evidence that it was clinically harmful.[17]

Case reports on adults have shown that iron dextran added to TPN is well tolerated and this might be due to the long infusion times.[18 19] Friel *et al*[4] administered intravenous iron dextran in parenteral nutrition solutions to very-low-birth-weight newborns in a randomised study. They found no difference between iron (200–250 µg/kg/day) and no iron in relation to infections during the 1-month study period. Another study regarding recombinant erythropoietin made by Ohls *et al*[5] gave iron dextran (1 mg/kg/day) in the TPN solution to very-low-birth-weight infants. The authors reported no adverse effects of EPO or iron. Both papers do not discuss possible destabilisation problems.

The European Medicines Agency's Committee for Medicinal Products for Human Use completed its review of intravenous iron-containing medicines in June 2013.[20] In the light of the limited data available, the Committee recommends further studies on the safety of intravenous iron medicines. One study by Meyer *et al*[21] compared oral and intravenous iron in preterm infants and concluded that intravenous iron appeared to be safe.

One concern of parenteral iron is iron overload. Serum ferritin should be monitored and adjusted accordingly. Unfortunately, we did not measure the S-ferritin at any time in our twin case, which would have been appropriate. If the blood sampling has to be kept to a strict minimum, a future alternative non-invasive method to monitor iron status could be measuring the hepcidin concentration in urine.[22]

Other concerns are that parenteral iron may increase the risk of sepsis in children who receive parenteral nutrition, but the evidence is sparse. One theory is that iron produces oxidative stress and stimulates bacterial growth.[10] Parenteral iron has been found to increase concentration of malondialdehyde (marker of lipid peroxidation) in preterm infants.[23] There was only one septic episode in our twin case; twin A had a sepsis that was due to a central venous catheter infection with confirmed coagulase-negative staphylococci in her blood culture.

In conclusion, our twin girls had different treatment courses in our attempt to avoid severe anaemia. Mixing the intravenous iron together with the parenteral nutrition was not performed purposely but apparently showed no severe adverse effect such as ROP, sepsis or lipid emboli. We did not search or test systematically for other adverse effects as we did not have a protocol for this. The practice should therefore not be considered as being safe based on this case report. In the future, stability tests are needed prior to iron infusion together with lipid-based parenteral nutrition.

Learning points

- In an attempt to avoid severe anaemia in Jehovah's Witness preterm infants, it is necessary to individualise the treatment course to maintain a good relationship between the parents and the medical staff. We wanted to insure a good fundament for the future relationship between the parents and their twin daughters.
- Following approaches can be considered in an attempt to avoid severe anaemia in Jehovah's Witness preterm infants: enteral or parenteral iron, folic acid, enteral or parenteral vitamin supplements, subcutaneous Erythropoietin, strict control of blood sampling and ward of court in order to give red blood cell transfusion.
- In our case report giving intravenous iron together with all-in-one parenteral nutrition and early treatment with erythropoietin went fortunately well, although there are known risks to intravenous iron as retinopathy of prematurity and oxidative injury, unknown risks (not reported/published) and unexpected risks (due to unfamiliar practice). We did not systematically search for adverse effects, and therefore the practice should not be considered as being safe based solely on this case report.

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REFERENCES

1 Domellof M, Braegger C, Campoy C, *et al*. Iron requirements of infants and toddlers: a position paper by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2014;58:119–29.
2 Kumpf VJ. Update on parenteral iron therapy. *Nutr Clin Pract* 2003;18:318–26.
3 Greene HL, Hambidge KM, Schanler R, *et al*. Guidelines for the use of vitamins, trace elements, calcium, magnesium, and phosphorus in infants and children receiving total parenteral nutrition: report of the Subcommittee on Pediatric Parenteral Nutrient Requirements from the Committee on Clinical Practice Issues of the American Society for Clinical Nutrition. *Am J Clin Nutr* 1988;48:1324–42.
4 Friel JK, Andrews WL, Hall MS, *et al*. Intravenous iron administration to very-low-birth-weight newborns receiving total and partial parenteral nutrition. *JPEN J Parenter Enteral Nutr* 1995;19:114–18.
5 Ohls RK, Harcum J, Schibler KR. The effect of erythropoietin on the transfusion requirements of preterm infants weighing 750 grams or less: a randomized, double-blind, placebo-controlled study. *J Pediatr* 1997;131:661–5.
6 Davis P, Herbert M, Davies DP. Case study. Erythropoietin for anaemia in a preterm Jehovah's Witness baby. *Early Hum Dev* 1992;28:279–83.
7 Horan M, Stutchfield PR. Severe congenital myotonic dystrophy and severe anaemia of prematurity in an infant of Jehovah's Witness parents. *Dev Med Child Neurol* 2001;43:346–9.
8 Marsal K, Persson PH, Larsen T, *et al*. Intrauterine growth curves based on ultrasonically estimated foetal weights. *Acta Paediatr* 1996;85:843–8.
9 pro.medicin.dk. Summary of Product Characteristics NeoRecormon. 22–2–2013. Ref Type: Online Source.
10 Koletzko B, Goulet O, Hunt J, *et al*. 1. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), supported by the European Society of Paediatric Research (ESPR). *J Pediatr Gastroenterol Nutr* 2005;41 (Suppl 2):S39–46.
11 Dickens BM, Cook RJ. Ethical and legal approaches to 'the fetal patient'. *Int J Gynaecol Obstet* 2003;83:85–91.
12 Nuffield council on bioethics. 2014. http://www.nuffieldbioethics.org/neonatal-medicine
13 Committee on Hospital Care. American Academy of Pediatrics. Family-centered care and the pediatrician's role. *Pediatrics* 2003;112(3 Pt 1):691–7.
14 Ohlsson A, Aher SM. Early erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. *Cochrane Database Syst Rev* 2012;9:CD004863.
15 Haiden N, Klebermass K, Cardona F, *et al*. A randomized, controlled trial of the effects of adding vitamin B12 and folate to erythropoietin for the treatment of anaemia of prematurity. *Pediatrics* 2006;118:180–8.
16 Driscoll DF, Bhargava HN, Li L, *et al*. Physicochemical stability of total nutrient admixtures. *Am J Health Syst Pharm* 1995;52:623–34.

17 Puntis JW, Rushton DI. Pulmonary intravascular lipid in neonatal necropsy specimens. *Arch Dis Child* 1991;66(1 Spec No):26–8.
18 Norton JA, Peters ML, Wesley R, *et al*. Iron supplementation of total parenteral nutrition: a prospective study. *JPEN J Parenter Enteral Nutr* 1983; 7:457–61.
19 Porter KA, Blackburn GL, Bistrian BR. Safety of iron dextran in total parenteral nutrition: a case report. *J Am Coll Nutr* 1988;7:107–10.
20 The European Medicines Agency's Committee for Medicinal Products for Human Use. Intravenous iron-containing medicinal products. 2013. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Intravenous_iron-containing_medicinal_products
21 Meyer MP, Haworth C, Meyer JH, *et al*. A comparison of oral and intravenous iron supplementation in preterm infants receiving recombinant erythropoietin. *J Pediatr* 1996;129:258–63.
22 Muller KF, Lorenz L, Poets CF, *et al*. Hepcidin concentrations in serum and urine correlate with iron homoeostasis in preterm infants. *J Pediatr* 2012;160:949–53.
23 Pollak A, Hayde M, Hayn M, *et al*. Effect of intravenous iron supplementation on erythropoiesis in erythropoietin-treated premature infants. *Pediatrics* 2001;107:78–85.