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Optimising neonatal management of haemolytic disease of the foetus and newborn

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Chapter six

Randomised controlled trial on the use of EPO to reduce postnatal transfusions in neonates with red blood cell alloimmunisation treated with intrauterine transfusions (protocol)

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In preparation

Abstract

Background

Up to 80% of infants with haemolytic disease of the foetus and newborn (HDFN) treated with intrauterine transfusion(s), require at least one postnatal transfusion for anaemia during the first 3 months of life. Erythropoietin (EPO) deficiency is considered a possible contributing factor to postnatal hyporegenerative anaemia in HDFN, and exogenous EPO administration may lower the postnatal transfusion-dependency in this population.

Objective

To evaluate the effect of darbepoetin alfa on the need for postnatal red blood cell transfusions in neonates with HDFN due to red cell alloimmunisation treated with IUT.

Study design

A total of 44 (near)-term infants admitted to the Leiden University Medical Centre (LUMC) with HDFN and treated with IUT will be included in this randomised controlled trial. Patients will be randomised to treatment with EPO (darbepoetin alfa, or Aranesp®) subcutaneously at a dosage of 10 µg/kg once a week for a period of 8 weeks (intervention), or "standard care". The primary outcome is the number of postnatal red blood cell transfusions required per infant after birth.

Discussion

The postnatal burden for infants affected by severe HDFN and their parents and caregivers is still high, with intensive follow-up after birth and often readmittance to hospital for one or multiple postnatal transfusions. This study evaluates the potential role for EPO-treatment in the postnatal management of HDFN.

Trial registration

Working title "EPO-4-Rh"-study, identifier NCT03104426, available at https://clinicaltrials.gov/ct2/show/NCT03104426.

Background

Haemolytic disease of the foetus and newborn (HDFN) is a condition in which maternal alloantibodies lead to the destruction of foetal erythrocytes. The mainstay of antenatal treatment of foetal anaemia HDFN is (serial) intrauterine transfusion (IUT).[1,2] The mainstay of postnatal treatment in HDFN is (1) intensive phototherapy and, if necessary, exchange transfusion to treat hyperbilirubinaemia and prevent kernicterus, and (2) postnatal transfusions to treat anaemia.[3]

Up to 88% of children with HDFN treated with IUT require at least one postnatal transfusion for anaemia during the first 3 months of life, with a median of two postnatal transfusions involving two hospital admissions per infant. [4-6] Postnatal anaemia can be divided in early (up to 7 days of life) anaemia due to ongoing haemolysis and late anaemia (7 days - 3 months of age). Late anaemia in neonates with HDFN may be due to depressed erythropoiesis (hyporegenerative anaemia) and/or persisting (intra-marrow) destruction of erythrocytes by remaining antibodies.[4,7,8] Hyporegenerative anaemia occurs in particular in neonates treated with several IUTs.[4,7,9] Other contributing factors for late anaemia have been reported such as severity of HDFN and the declining use of exchange transfusions (hence less removal of maternal alloantibodies from the neonatal circulation).[3] Finally, erythropoietin (EPO) deficiency is also considered as a possible contributing factor to late anaemia.[10-15]

It has been postulated that there is an insufficient response in increase of EPO levels, and exogenous EPO has been increasingly used in full-term and preterm children to prevent or reduce neonatal anaemia without short or long-term adverse effects.[14,16-18] Several small studies and casuistic reports suggest that children with HDFN may benefit from treatment with EPO to reduce the risk of anaemia and subsequent transfusions.[10-15] However, other authors found that EPO may be less effective than expected.[19] Due to the lack of evidence, routine use of EPO is currently not recommended.[3] To determine a role for administration of EPO in this group of patients, a randomised controlled clinical trial of sufficient sample size is required to evaluate the effect of exogenous EPO on the prevention of postnatal anaemia in HDFN, as potential alternative for red blood cell transfusions.[15] Potentially, EPO drives production of erythropoiesis leading to stabilisation of the haemoglobin levels of these children. EPO administration may thus prevent occurrence of late anaemia, hospital admissions for transfusions and potential transfusion reactions, creating a more stable and natural postnatal course for patients with HDFN. In this scenario, the current management of weekly out-patient visits and weekly blood draws for haemoglobin level measurements, may be reduced, further contributing to reduction of the burden for these children.

Methods

Objective

The primary objective of this study is to investigate whether EPO is effective in reducing the incidence of late anaemia in children with HDFN treated with IUT, and therefore in decreasing the number of postnatal transfusions per child, compared to a control group of children receiving standard care without darbepoetin alfa (or Aranesp®, a long acting agent of EPO) treatment.

Study population

All (near) term children (gestational age ≥ 35 weeks) with HDFN (due to D, C, c, E, K or other red blood cell alloimmunisation) treated with IUT and admitted to the Leiden University Medical Centre (LUMC) after October 2017 are eligible for the study. The LUMC is the single national referral centre in the Netherlands for pregnancies complicated by maternal red blood cell alloimmunisation. A prenatal national screening program in the Netherlands indicates referral to the LUMC in case of elevated antibody titres tested in maternal serum ≥1/2 in K immunisation and ≥1/16 in D or other types of alloimmunisation or in case of an elevated antibody-dependent cell-mediated cytotoxicity (ADCC) assay ≥ 50% in case of D immunisation and ≥ 30% in case of other blood group antigens. These pregnancies are monitored by serial Doppler measurements to assess the velocity of the middle cerebral artery (MCA), which is considered the most accurate non-invasive predictor of foetal anaemia. If MCA Doppler exceeds 1.5 multiples of the median, or if signs of hydrops are present, treatment with IUT is indicated. Intrauterine transfusion is usually continued until 34-35 weeks' gestation to progress these pregnancies to term.[20] In general, labour and admission of the child to the Neonatology department of the LUMC is highly recommended in these pregnancies. Approximately 15 eligible patients are treated in the LUMC annually.

Transfusion policy

Postnatal anaemia in this study is defined as a need for one or more erythrocyte transfusions. The LUMC transfusion guideline recommends a postnatal transfusion of 15 ml/kg irradiated erythrocytes in full-term neonates with HDFN when haemoglobin levels fall below 10.5 g/dL (6.5 mmol/L, day 0-6), below 8.9 g/dL (5.5 mmol/L, day 7-13) and below 7.2 g/dL (4.5 mmol/L, from day 14). These cut-off values are communicated with referral hospitals after discharge from the LUMC and the research team is in contact with these hospitals to ensure transfusions are given according to these cut-off values.

Study design

The EPO-4-Rh study is a single centre randomised controlled trial. The trial is registered with ClinicalTrials.gov, identifier NCT03104426. Included children are randomised at birth to treatment with darbepoetin alfa (intervention group) or "standard care", with 1:1 allocation, to be randomised in varying blocks of 4 and 6, no stratification is applied. In the treatment group, darbepoetin alfa is administered subcutaneously at a dosage of 10 μg/kg once a week, starting at approximately day 7, for a period of 8 weeks. Treatment is administered during weekly home visits in the treatment arm after discharge from the LUMC. No concomitant therapy with folate (0.25 mg/day) is given (standard practice), concomitant iron therapy is given if ferritin level drops below 75 microg/l (standard practice). Weekly routine measurements of complete blood counts (including haemoglobin level, haematocrit and reticulocyte count) will be performed in both groups (standard practice). EPO is discontinued if haemoglobin level is ≥ 13 g/dL after at least 4 weeks of treatment with EPO. In EPO-treated children, blood pressure will be measured for safety reasons at onset of treatment, after four weeks and eight weeks. Monthly measurements of liver enzymes (aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), gamma-glutamyl transferase (γGT) and lactate dehydrogenase (LDH)) will also be performed in all groups (standard practice). In addition, the neonatal EPO-level will be determined at birth in both groups. The number of postnatal transfusions received during the first 3 months of life and haemoglobin levels prior to the postnatal transfusion are recorded. After initial discharge from the LUMC, postnatal red blood cell transfusions are recommended to be performed when haemoglobin levels fall below aforementioned cut-off values of haemoglobin. Because of these clearly defined guideline and haemoglobin measures, blinding of caregivers to treatment allocation and use of a placebo was not deemed necessary.

Data collection

Collected data, including history of pregnancy, neonatal clinical records from the initial hospitalisation at the LUMC, and records from additional admissions and outpatient clinic visits in other hospitals than the LUMC, are collected for each included patient with written consent of parents or caregivers. Data are upon collection blinded and entered into an online secured database (CASTOR) by a member of the research team with in this database blinding of treatment allocation. The data manager and statistician involved are blinded as well. After all data is collected and entered in the database, and after data cleaning, the database will be locked and the data will be unblinded to all parties involved.

End points

The primary end point is the number of postnatal red blood cell transfusions per child from birth up to 3 months of life. Secondary end points are: the percentage of children requiring a postnatal transfusion up to 3 months of life; time from birth to first postnatal transfusion (days); haemoglobin level at first postnatal transfusion (g/dL); number of days of hospitalisation and readmission(s) associated with erythrocyte transfusion(s); course of haemoglobin up to 3 months of life.

Sample size calculation

Based on the (scarce) results in the literature, we expect a 50% reduction in the median number of total postnatal red blood cell transfusions per patient with EPO treatment, from a median of 2 to 1. For sample size calculation we hypothesised a shift in the distribution of number of transfusions per child as depicted in Figure 1. The distribution in the 'care as usual' group are based on data from 2000-2014. Based on these expected frequencies, group sample sizes of 21 infants achieve 81% power to detect a difference of 1.1 between the null hypothesis that both group means are 1.9 and the alternative hypothesis that the mean of the EPO group is 0.8 with estimated group standard deviations of 1.5 and 0.9 and with a significance level (alpha) of 0.05 using a two-sided Mann-Whitney test. The drop-out percentage is estimated at 5%, adding (42/0.95 = 44) 1 child to each group's sample size.

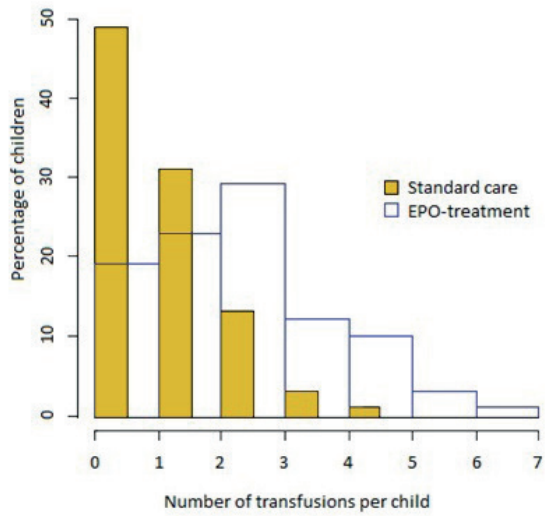

Figure 1. Hypothesised distribution of number of postnatal transfusions

Discussion

The postnatal burden for children affected by severe HDFN and their parents and caregivers is still high, with intensive follow-up after birth and often readmittance to hospital for one or multiple postnatal transfusions. Of children treated with IUT, 88% receives one or more red blood cell transfusions, with a median of two transfusions per child, although some children require up to six transfusions after birth.[6] The number of postnatal transfusions does not show a decline over time with improvement of neonatal care.[5,6] This randomised controlled study evaluates the potential role for EPO (darbepoetin alfa) in the postnatal course of HDFN, and will determine whether EPO is an effective agent to reduce postnatal transfusion dependency and medicalisation of these patients.

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