Study on Transfusion Effects in Preterm infants

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational non invasive

Summary

ID

NL-OMON48979

Source
ToetsingOnline

Brief title
STEP-trial

Condition

- Other condition
- Anaemias nonhaemolytic and marrow depression
- Gastrointestinal inflammatory conditions

Synonym
Anemia and low red blood cell count

Health condition

neurologische ontwikkeling

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: anemia/hypoxia, erythropoietin, preterm infants, red blood cell transfusion

Outcome measures

Primary outcome

The primary outcome measure will be epo regulation and expression at various ages: baseline epo concentration in umbilical cord blood, baseline DNA methylation and gene expression in placental tissue, epo concentration in blood at the age of two weeks after birth, the degree of DNA methylation in intestinal cells isolated from feces at the age of two weeks after birth, and the degree of DNA methylation in intestinal cells isolated from feces at the age of three to six months post-term. Additionally, if one of the included infants developed NEC and needs surgery, then a small part of the removed intestine will be analysed in laboratory for intestinal epo gene expression. Furthermore, we will use Hb levels assessed during standard care and collect information (number and volume) regarding RBC transfusions during the first four weeks of life. Cerebral and intestinal oxygen saturation during the first four weeks after birth and urinary isoprostane concentrations will also be determined.

Secondary outcome

Secondary outcomes will be cerebral and intestinal tissue oxygen saturation, urinary intestinal fatty acid binding protein concentration before and after

RBC transfusion, and the prevalence of NEC and its grading up to 40 weeks postmenstrual age. Furthermore, we will assess the neurological condition using the assessment of general movements (GMs) before and after the first RBC transfusion, and the neurological outcome at the age of three months (+/- 2 weeks) post-term, based on the motor optimality score (MOS) of the quality of the GMs.

Study description

Background summary

Neonatal anemia is common in preterm infants. Anemia may lead to hypoxia, possibly resulting in cell damage. A red blood cell (RBC) transfusion is an intervention aiming to rapidly improve oxygen transport to vital organs, such as the brain and the gut.
Anemia and RBC transfusions result in low and high organ oxygenation respectively. Both might be harmful, and especially high variation in oxygenation may lead to damage in vulnerable organs, such as the brain and the gut. As erythropoiesis is partly upregulated by hypoxia, there might be an association between these oxygenation values and the expression of erythropoietin (epo), which is the essential growth factor for the production of erythrocytes. Also, the expression of the epo receptor in the intestinal enterocytes might influence growth and development of the gastrointestinal tract, which may protect against necrotizing enterocolitis (NEC) in preterm born infants. Epo may also provide neuroprotection for different pathways of brain injury. In the brain, epo, therefore functions as both an important growth factor and a neuroprotective agent.
The expression of epo is controlled by DNA methylation. DNA methylation, i.e. adding a methyl group to the DNA molecules, results in inactivity of the gene. This DNA methylation has been shown to partially depend on oxygen and nutrient supply. Anemia leads to decreased oxygen transport and decreased organ oxygenation, whereas RBC transfusion increases oxygenation. It is unknown whether anemia and/or RBC transfusion are related to the expression of epo in gut cells through these various levels of oxygenation. We will therefore explore whether epo regulation and expression in intestinal cells may be associated with the course of hemoglobin (Hb) levels. Furthermore, we will explore if epo regulation and expression may also be associated with anemia, RBC transfusions, oxidative stress, and organ oxygenation in the neonatal period. Secondary, we will evaluate the clinical consequences and the

neurological outcome of the variable oxygenation levels.

Study objective

The first objective is to explore whether epo regulation and expression, at the age of two weeks after birth and three to six months post-term, are associated with the course of Hb levels. Furthermore, we will assess if epo regulation and expression are also associated with anemia, RBC transfusions, oxidative stress, and cerebral and intestinal oxygenation in preterm infants during the early neonatal period.
Our second objective is to evaluate the association between various oxygenation levels and hypoxic intestinal cell damage, the prevalence of NEC and its grading up to 40 weeks postmenstrual age, the neurological condition during anemia and after RBC transfusion, and the neurological outcome at three months post-term.

Study design

Prospective observational cohort study.

Study burden and risks

This study cannot be performed in another population, as the lack of knowledge about the possible association between anemia and RBC transfusions, and the expression of epo in gut cells, through the various levels of oxygenation is typical for preterm infants.

Burden: All infants participating in the study are subjected to routine neonatal intensive care. This study is an observational study, implying minimal extra care; therefore there is minimal burden and risk associated with participation.
First, the fecal samples will be collected from the diaper, using a scooper. The samples will be collected during routine handling moments, so the infant will not be disturbed. Parents will be asked to send a feces sample of their infant around the age of three to six months post-term. They will receive a kit, which contains a preservation buffer. The stool sample is stable at room temperature for months and can be send by mail.
Second, we intend to measure the epo concentration in the second week of life to validate the DNA methylation in the fecal samples, by sampling 100 microliter extra blood, which is about three drops, only when blood will be drawn for clinical purposes. The 100 microliter umbilical cord blood will be sampled after birth.
Third, monitoring of cerebral and intestinal regional tissue oxygen saturation is routine clinical care in all preterm infants admitted to the NICU at the UMCG, and near-infrared spectroscopy (NIRS) is a continuous and non-invasive method to use. For the purpose of this study possibly extra NIRS measurements

will be needed in the third and fourth week of life, during the time around and after the infant receives an RBC transfusion.
Fourth, the urinary samples will be collected non-invasively by a small gauze in the diaper. The samples will be collected during routine handling moments, so the infant will not be disturbed.
Fifth, evaluating GMs is a widely accepted non-invasive method to assess the neurological neonatal outcome. Before and after the first RBC transfusion the infant will be video-recorded for 30 minutes, and at the age of three months (+/- 2 weeks) post-term for 10 minutes, with the infant in an actively awake state, comfortably dressed, with uncovered arms and legs. The camera will be placed in a way that caregivers are not hindered by the camera and do not lose sight on the monitor. Therefore, video recording GMs will not interfere with clinical care.

Benefits and risks: The study may provide more insight in the mechanism of the epo regulation and expression, as a neuroprotective agent, and as a factor influencing growth and development of the gastrointestinal tract. It may elucidate the relation between epo regulation and expression on the one hand and anemia and RBC transfusions and subsequent oxygenation of organs on the other. This might be of importance for a normal neurological development and to prevent NEC, increasing quality of life of preterm infants.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

- gestational age < 32 weeks
- before 7 days of age
- written informed consent by legal representative(s)

Exclusion criteria

- Chromosomal abnormality (e.g. trisomy 13, 18, 21)
- Perinatal asphyxia resulting in Apgar score (AS) < 5 at five minutes postpartum
- Major congenital malformations that increase the risk of death or adverse neurodevelopmental outcome (congenital cerebral malformations, congenital heart diseases excluding patent ductus arteriosus)
- Intraventricular and periventricular hemorrhage > grade 2 according to Papile, prior to inclusion
- Diagnosis of NEC prior to inclusion
- Alloimmune hemolytic disease, sickle-cell disease or thalassemia
- Any received RBC transfusions prior to inclusion
- Inability to understand Dutch by the parents
- Parents expressing strong philosophical or religious objections to transfusion

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-03-2019
Enrollment:	67
Type:	Actual

Ethics review

Approved WMO Date:	10-10-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-12-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-01-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-03-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 29247
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL62348.042.17
Other	NTR 6625 / NL6447